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(54) **ADENO-ASSOCIATED VIRUS COMPOSITIONS FOR RESTORING PAH GENE FUNCTION AND METHODS OF USE THEREOF**

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(51) **Int. Cl.**

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C12N 15/12	(2006.01)
C12N 15/86	(2006.01)
C12N 15/90	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 48/0066*** (2013.01); ***A61K 38/44*** (2013.01); ***C12N 15/86*** (2013.01); *C12N 2750/14143* (2013.01); *C12N 2750/14151* (2013.01); *C12N 2830/50* (2013.01); *C12Y 114/16001* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Provided herein are recombinant adeno-associated virus (rAAV) compositions that can restore phenylalanine hydroxylase (PAH) gene function in cells, and methods for using the same to treat diseases associated with reduction of PAH gene function (e.g., PKU). Also provided are nucleic acids, vectors, packaging systems, and methods for making the adeno-associated virus compositions.

18 Claims, 40 Drawing Sheets

Specification includes a Sequence Listing.

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FIG. 1

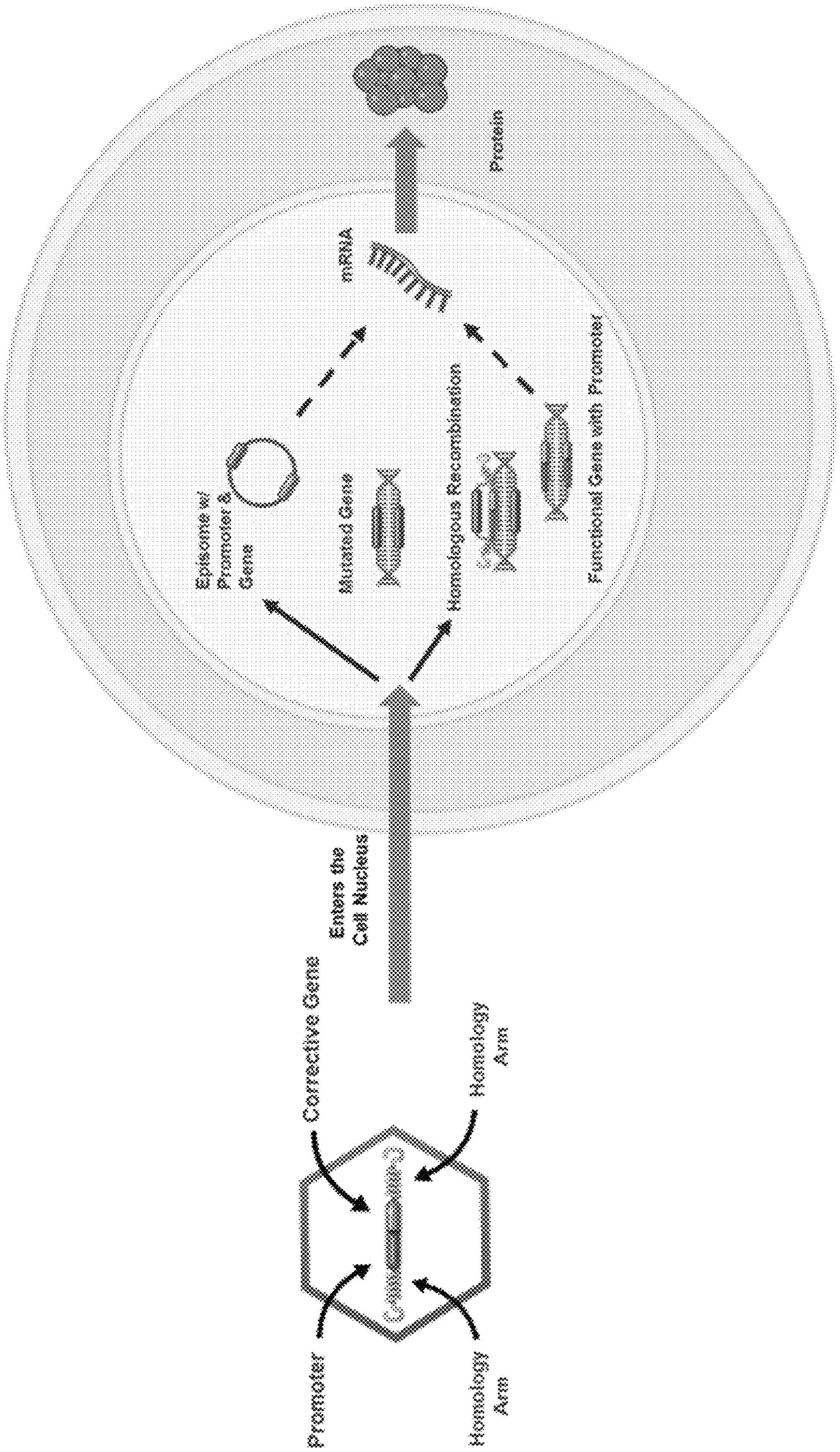
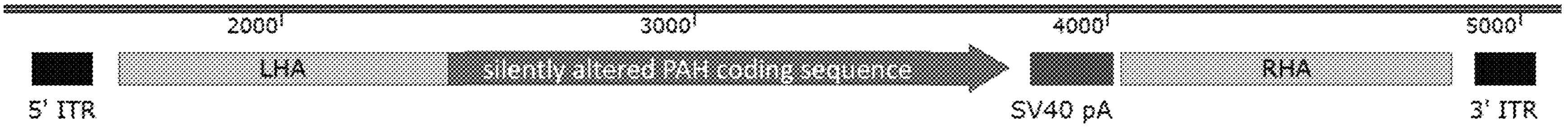

Promoter
Homology Arm
Corrective Gene
Homology Arm
Enters the Cell Nucleus
Episome w/ Promoter & Gene
Mutated Gene
Homologous Recombination
Functional Gene with Promoter
mRNA
Protein

FIG. 2A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3000
4000
5000
LHA
silently altered PAH coding sequence
RHA
5' ITR
SV40 pA
3' ITR

FIG. 2B

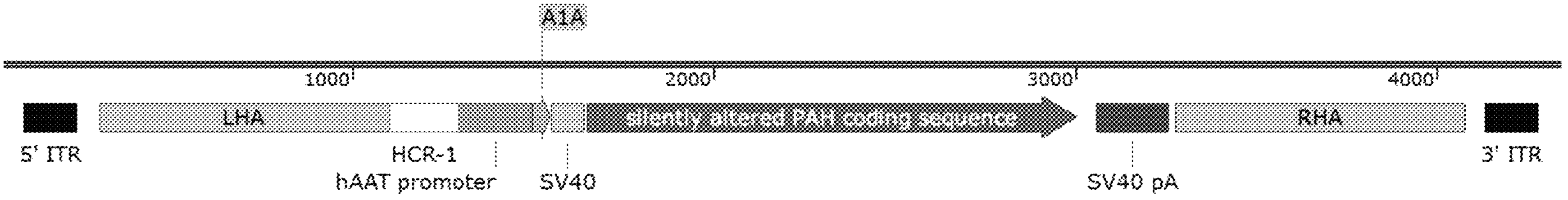

A1A
1000
2000
3000
4000
LHA
silently altered PAH coding sequence
RHA
5' ITR
HCR-1
hAAT promoter
SV40
SV40 pA
3' ITR

FIG. 2C

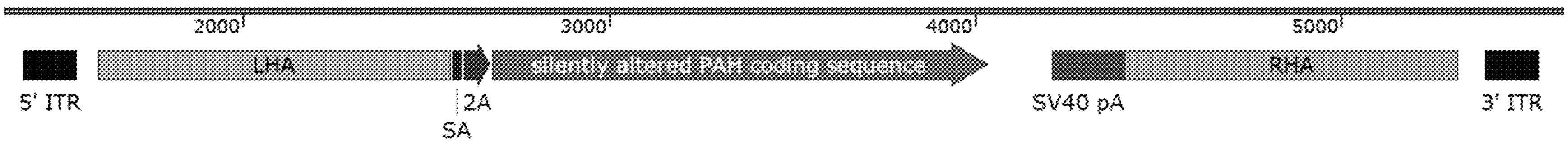

2000
3000
4000
5000
LHA
silently altered PAH coding sequence
RHA
5' ITR
2A
SA
SV40 pA
3' ITR

FIG. 2D

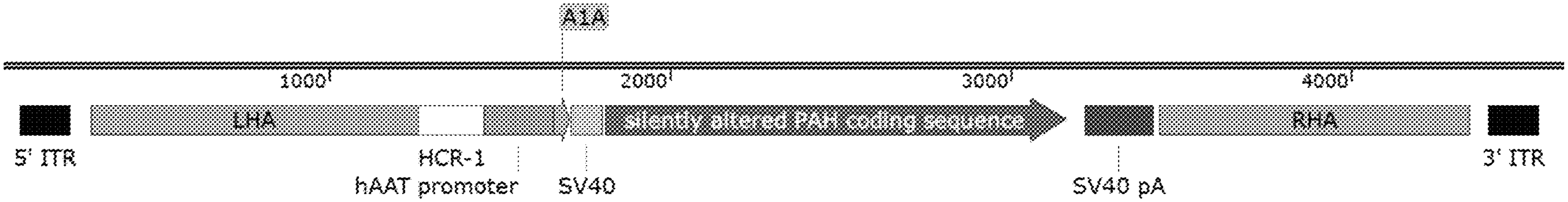

A1A
1000
2000
3000
4000
LHA
silently altered PAH coding sequence
RHA
5' ITR
HCR-1
hAAT promoter
SV40
SV40 pA
3' ITR

FIG. 3

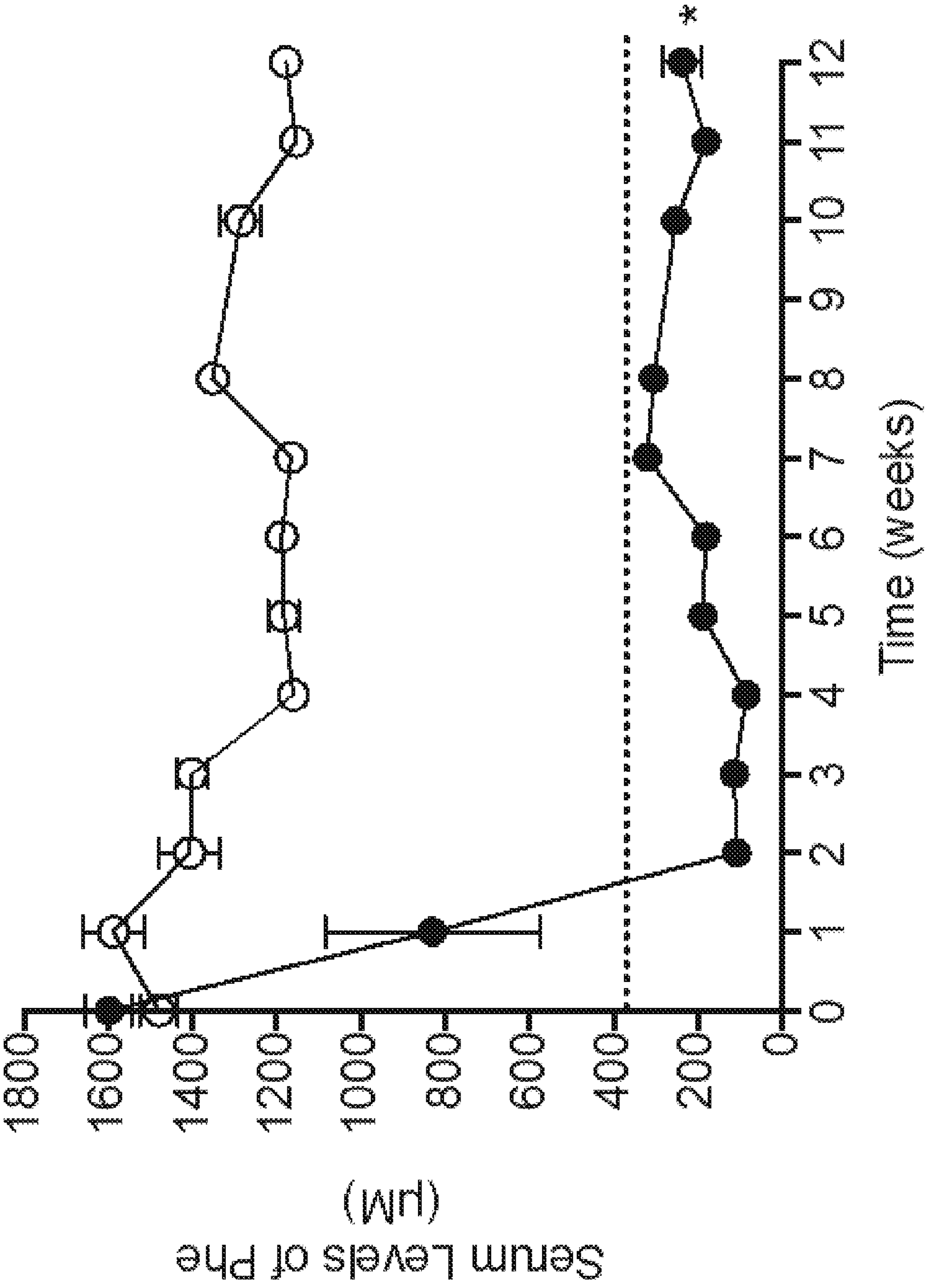

Serum Levels of Phe (μM)
1800
1600
1400
1200
1000
800
600
400
200
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (weeks)
*

FIG. 4

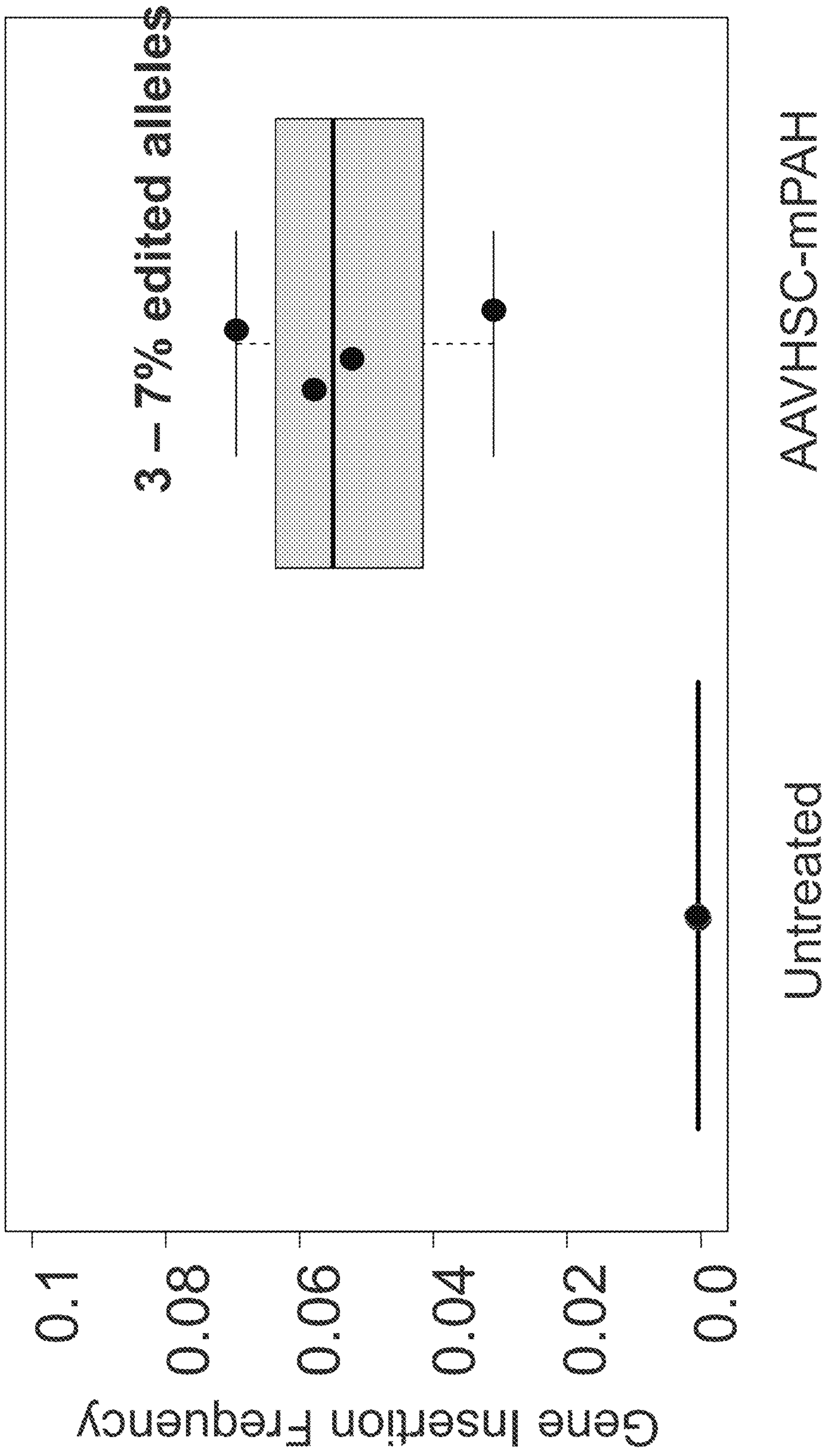

3 – 7% edited alleles
Gene Insertion Frequency
0.1
0.08
0.06
0.04
0.02
0.0
Untreated
AAVHSC-mPAH

FIG. 5

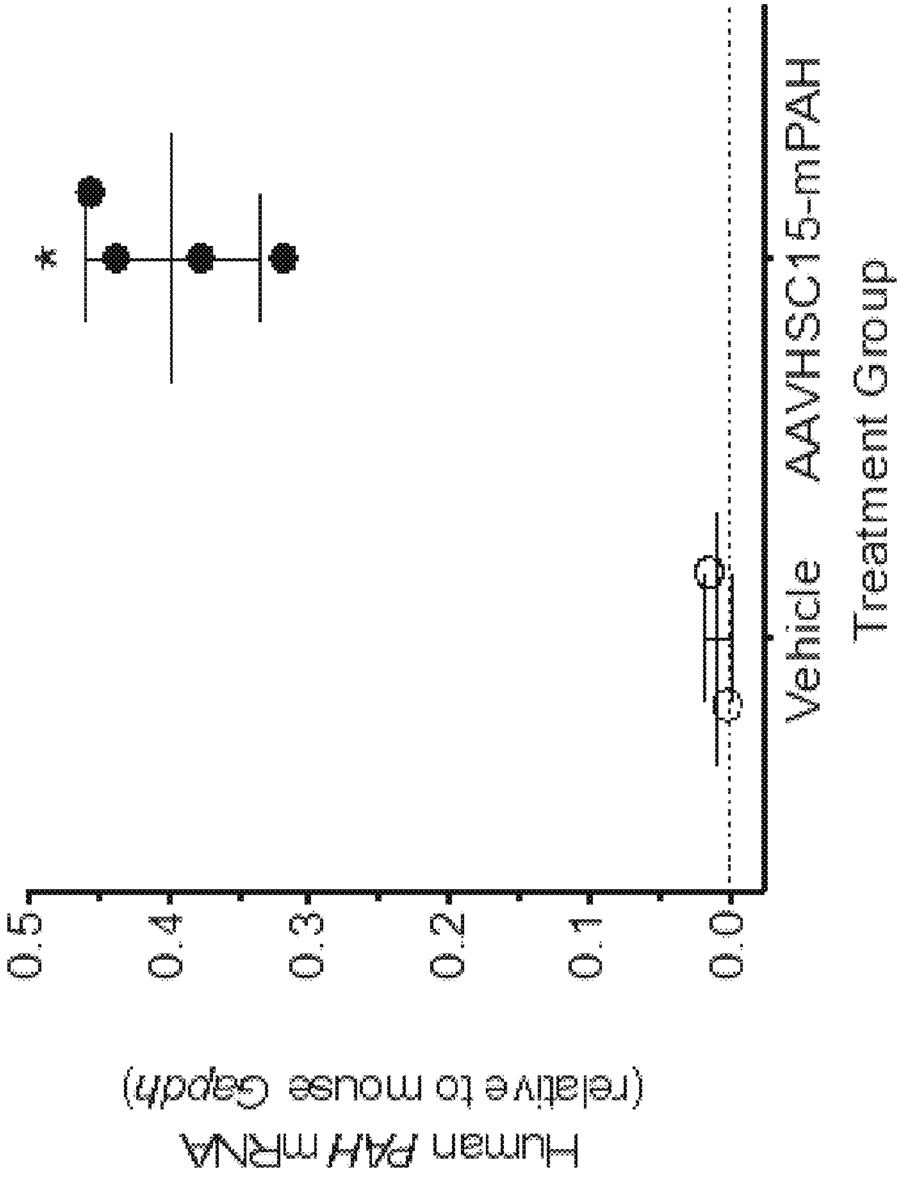

Human *PAH* mRNA
(relative to mouse *Gapdh*)
0.5
0.4
0.3
0.2
0.1
0.0
*
Vehicle
AAVHSC15-mPAH
Treatment Group

FIG. 6

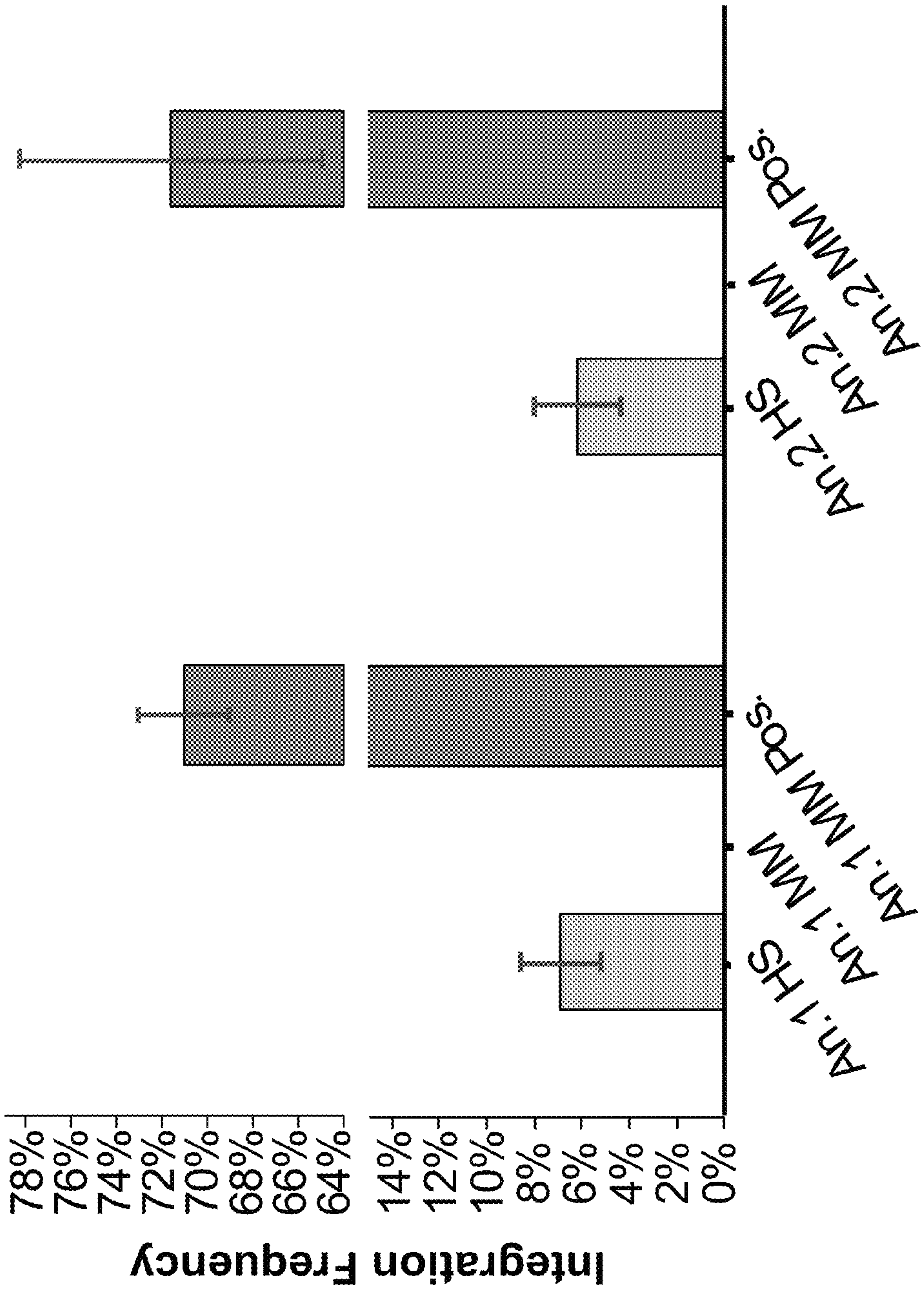

Integration Frequency
78%
76%
74%
72%
70%
68%
66%
64%
14%
12%
10%
8%
6%
4%
2%
0%
An.1 HS
An.1 MM
An.1 MM Pos.
An.2 HS
An.2 MM
An.2 MM Pos.

FIG. 7

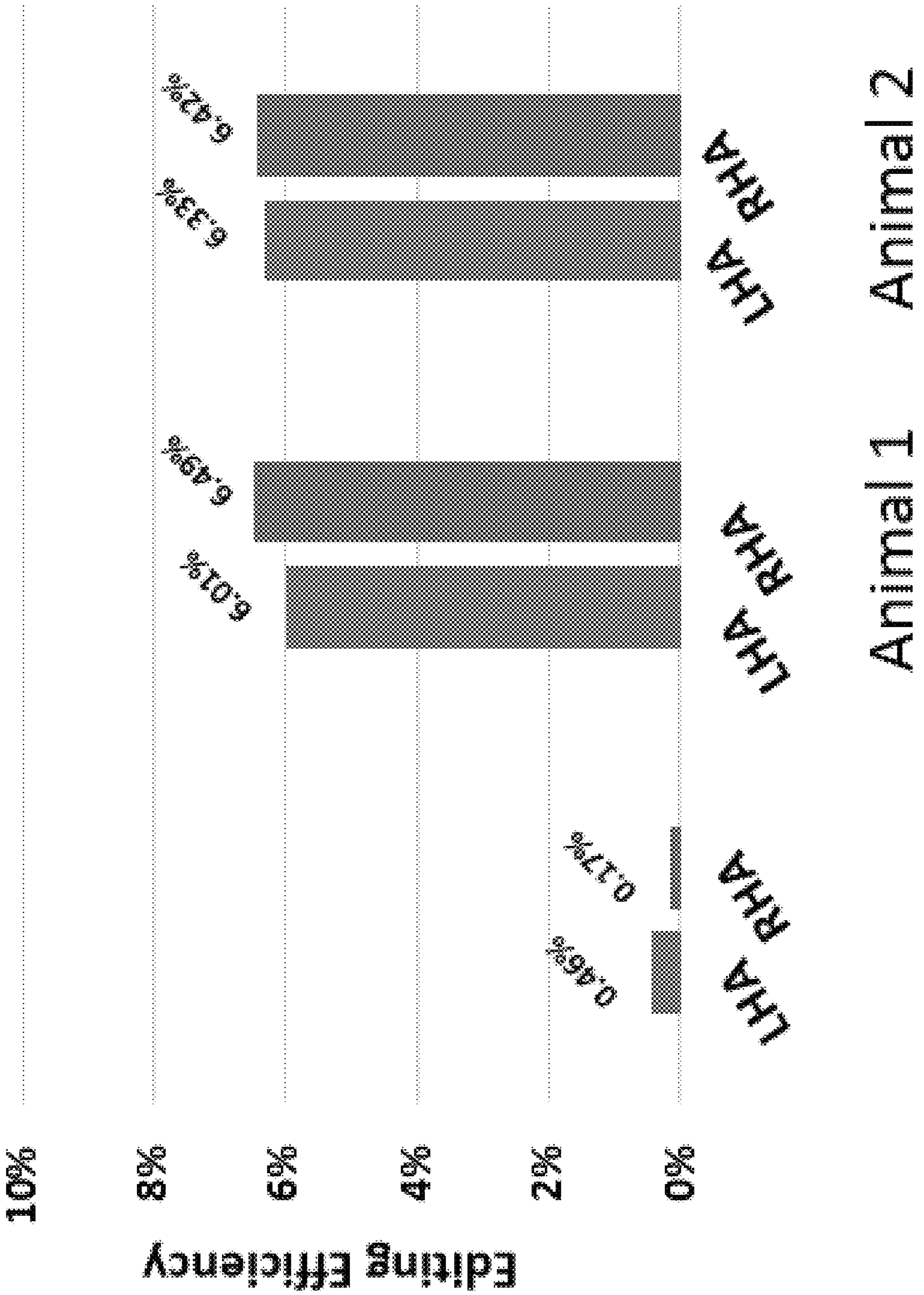

Editing Efficiency
10%
8%
6%
4%
2%
0%
0.46%
0.17%
6.01%
6.49%
6.33%
6.42%
LHA
RHA
LHA
RHA
Animal 1
LHA
RHA
Animal 2

FIG. 8A

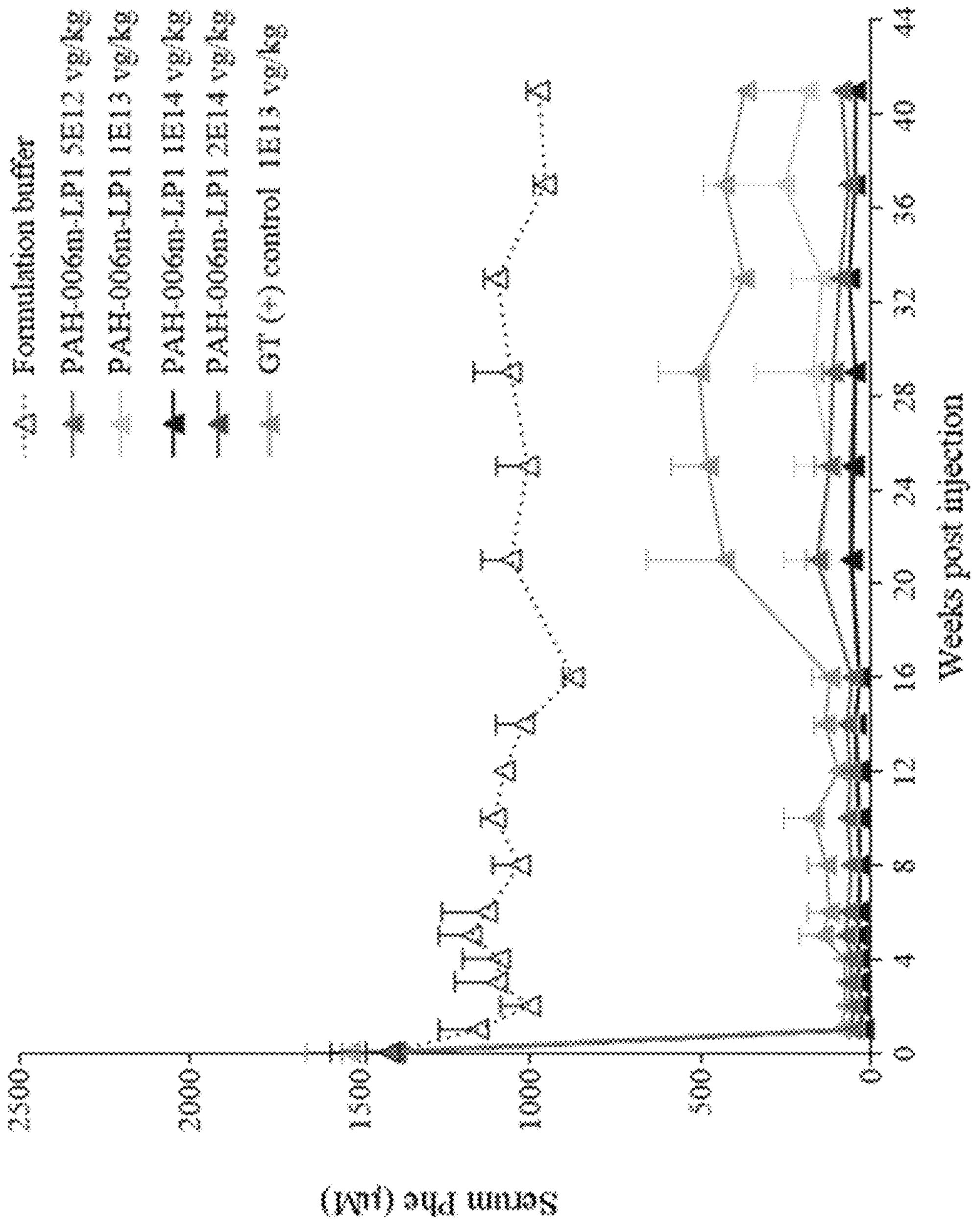

Formulation buffer
PAH-006m-LP1 5E12 vg/kg
PAH-006m-LP1 1E13 vg/kg
PAH-006m-LP1 1E14 vg/kg
PAH-006m-LP1 2E14 vg/kg
GT (+) control 1E13 vg/kg
Serum Phe (μM)
2500
2000
1500
1000
500
0
Weeks post injection
0
4
8
12
16
20
24
28
32
36
40
44

FIG. 8B

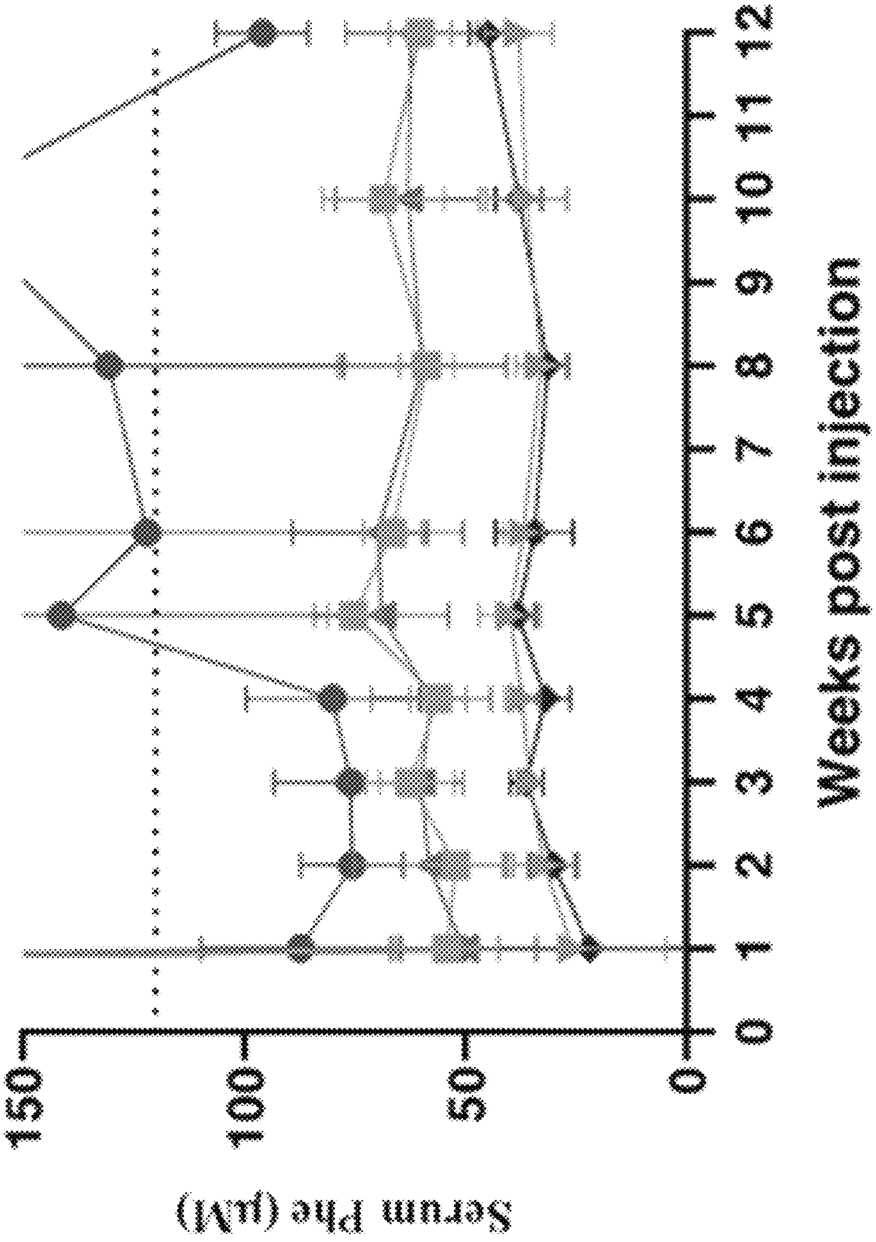

Serum Phe (µM)
150
100
50
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Weeks post injection

FIG. 8C

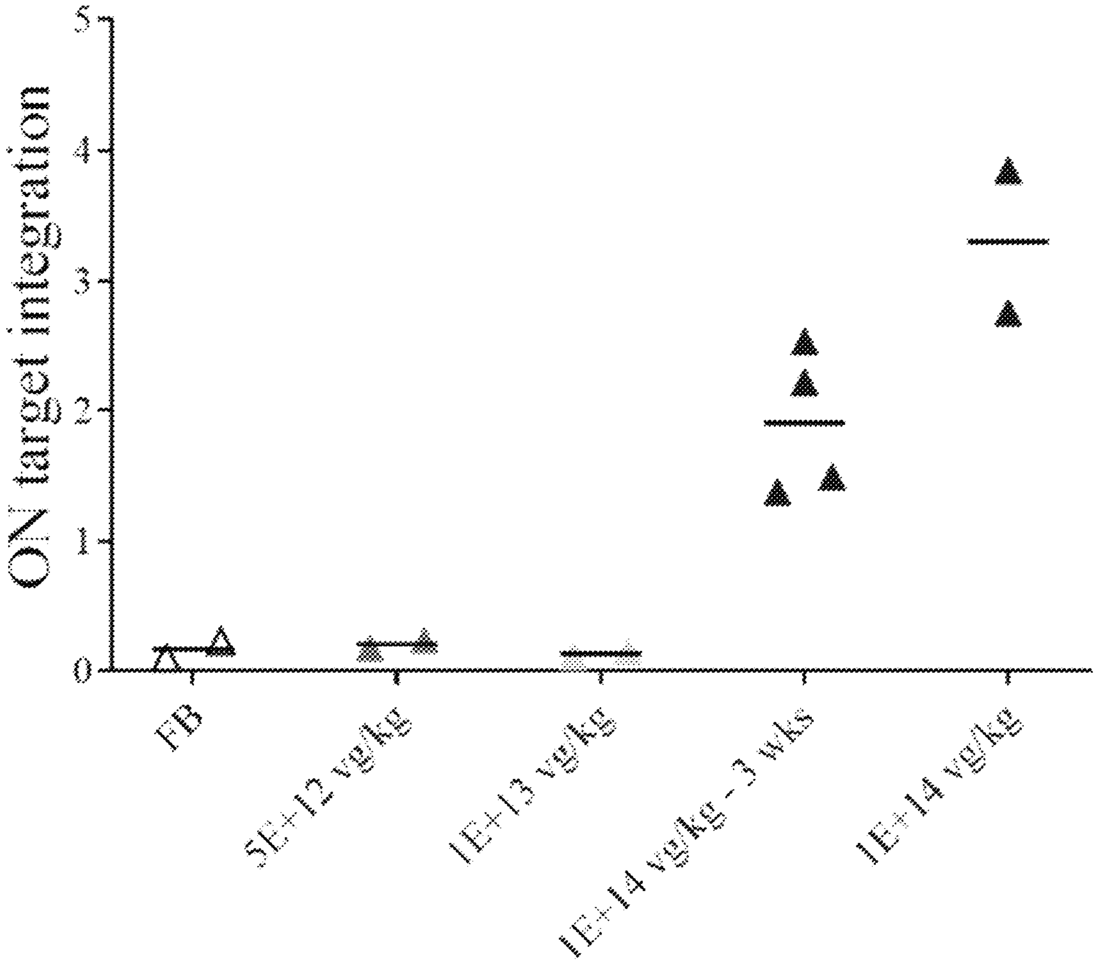

ON target integration
0
1
2
3
4
5
FB
5E+12 vg/kg
1E+13 vg/kg
1E+14 vg/kg - 3 wks
1E+14 vg/kg

FIG. 9A

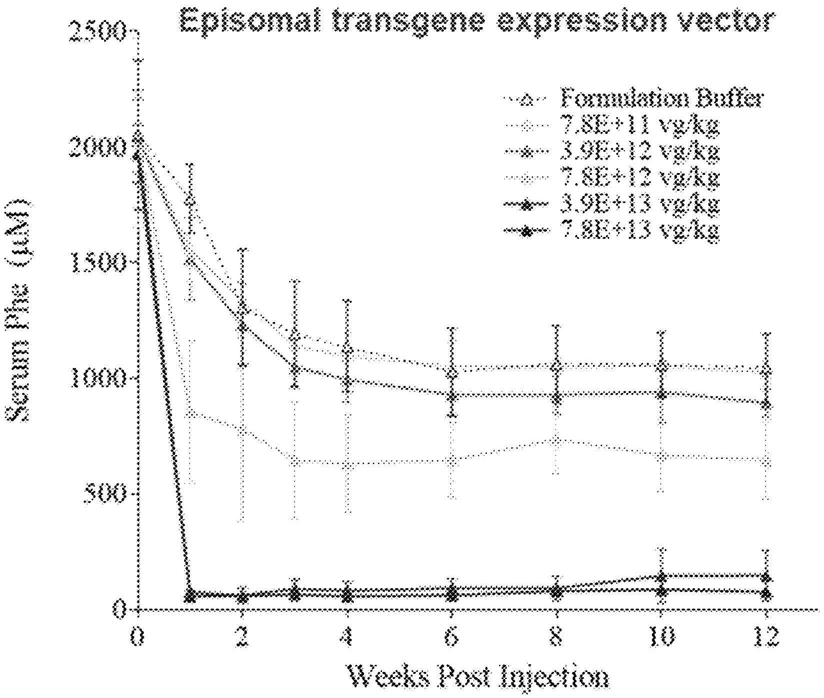

Episomal transgene expression vector
Serum Phe (μM)
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
Weeks Post Injection
Formulation Buffer
7.8E+11 vg/kg
3.9E+12 vg/kg
7.8E+12 vg/kg
3.9E+13 vg/kg
7.8E+13 vg/kg

FIG. 9B

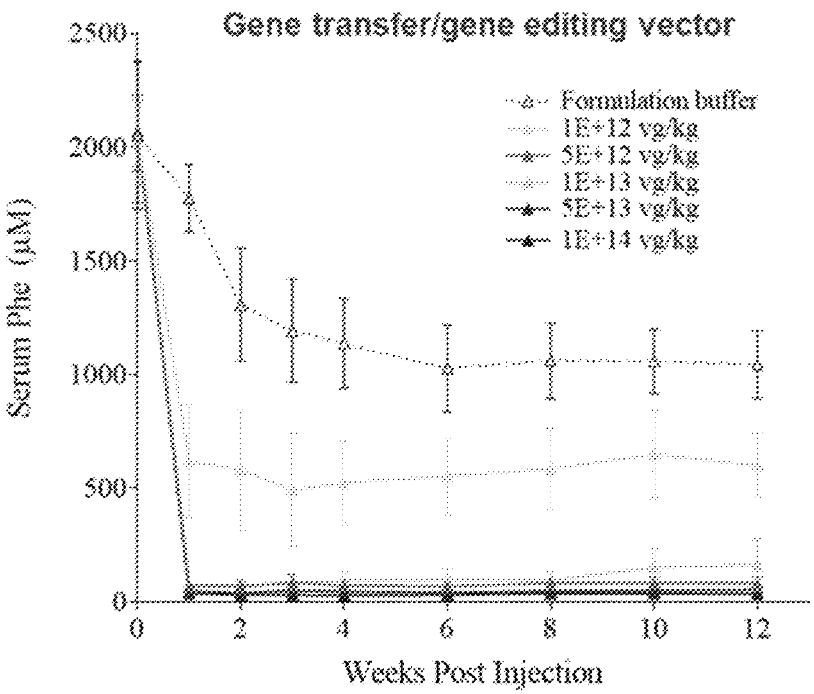

Gene transfer/gene editing vector
Serum Phe (μM)
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
Weeks Post Injection
Formulation buffer
1E+12 vg/kg
5E+12 vg/kg
1E+13 vg/kg
5E+13 vg/kg
1E+14 vg/kg

FIG. 9C

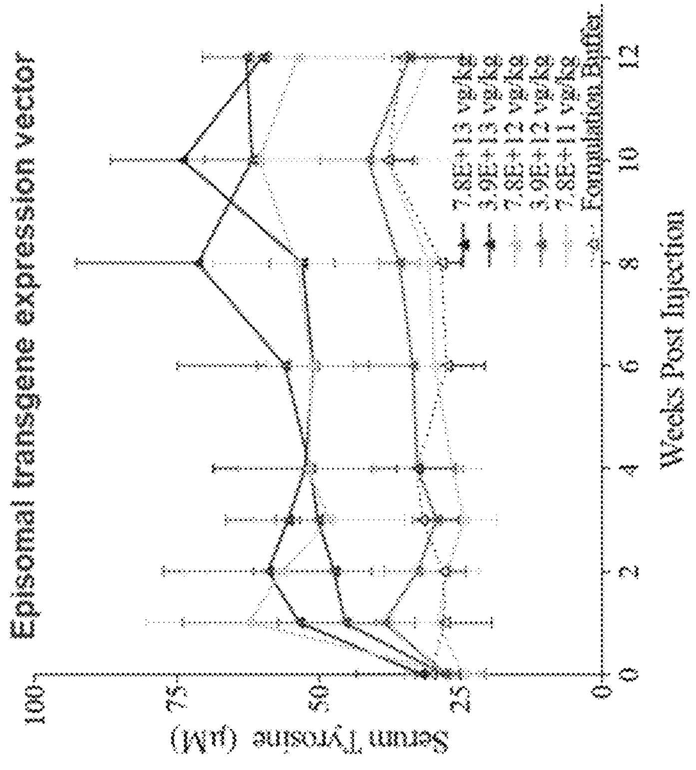

Episomal transgene expression vector
Serum Tyrosine (μM)
0
25
50
75
100
Weeks Post Injection
0
2
4
6
8
10
12
7.8E+13 vg/kg
3.9E+13 vg/kg
7.8E+12 vg/kg
3.9E+12 vg/kg
7.8E+11 vg/kg
Formulation Buffer

FIG. 9D

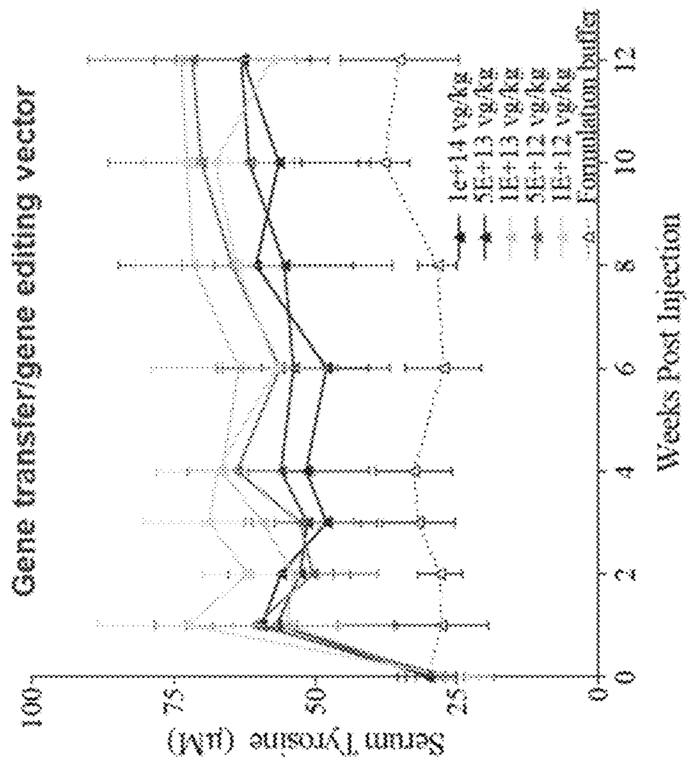

Gene transfer/gene editing vector
Serum Tyrosine (μM)
0
25
50
75
100
Weeks Post Injection
0
2
4
6
8
10
12
1e+14 vg/kg
5E+13 vg/kg
1E+13 vg/kg
5E+12 vg/kg
1E+12 vg/kg
Formulation buffer

FIG. 9E

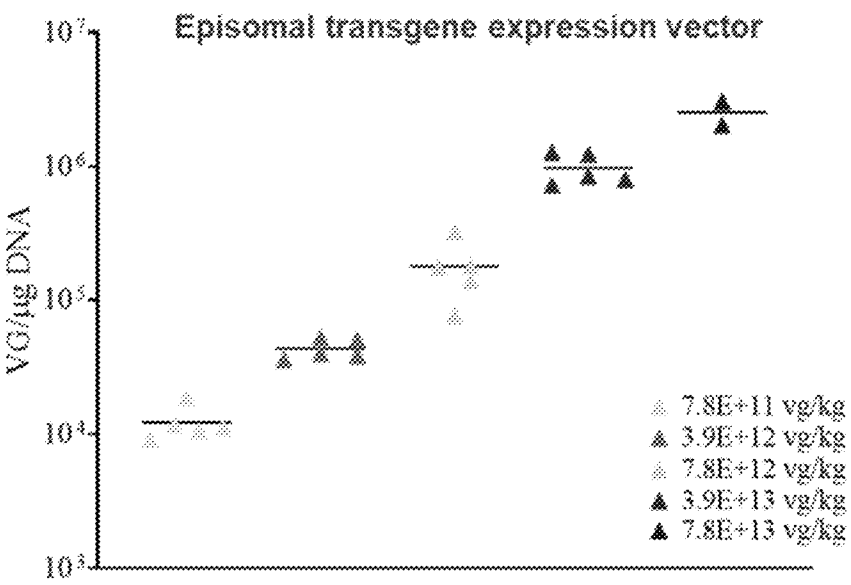

Episomal transgene expression vector
VG/μg DNA
10^7
10^6
10^5
10^4
10^3
7.8E+11 vg/kg
3.9E+12 vg/kg
7.8E+12 vg/kg
3.9E+13 vg/kg
7.8E+13 vg/kg

FIG. 9F

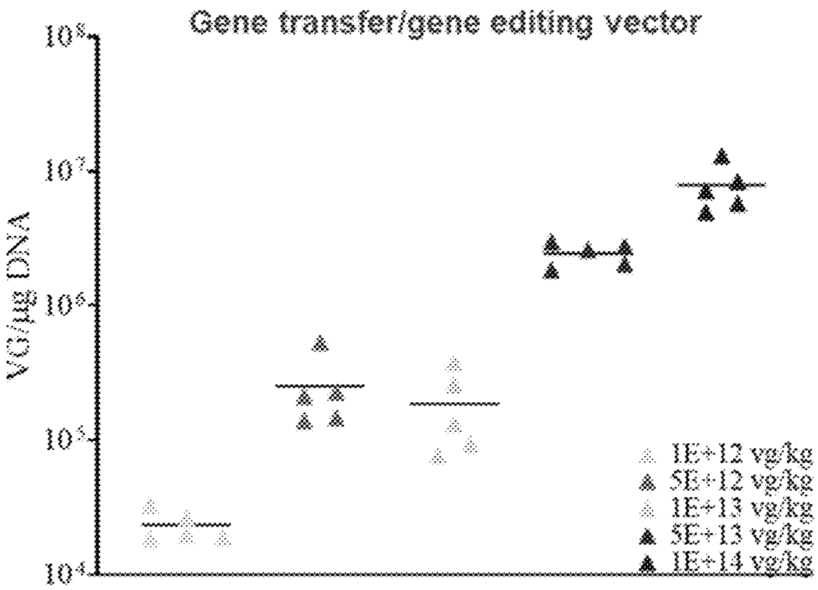

Gene transfer/gene editing vector
VG/μg DNA
10^8
10^7
10^6
10^5
10^4
1E+12 vg/kg
5E+12 vg/kg
1E+13 vg/kg
5E+13 vg/kg
1E+14 vg/kg

FIG. 9G

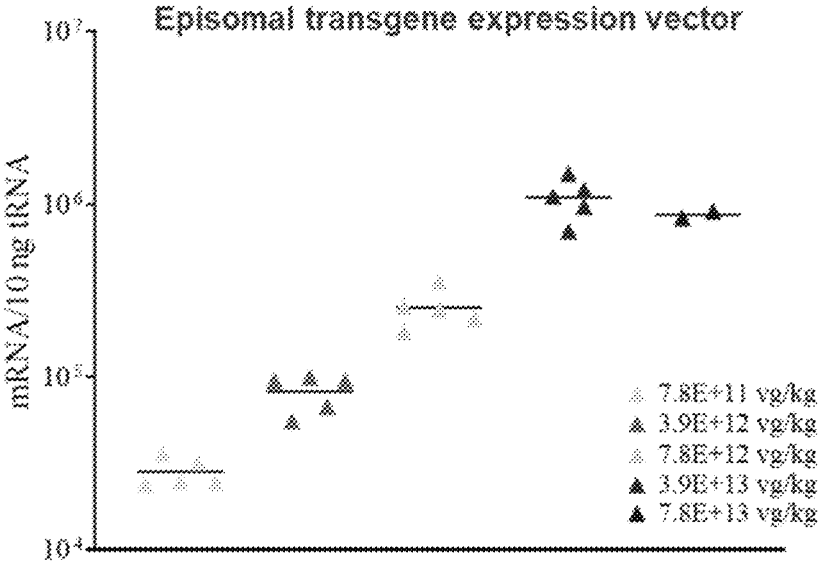

Episomal transgene expression vector
mRNA/10 ng tRNA
10^7
10^6
10^5
10^4
7.8E+11 vg/kg
3.9E+12 vg/kg
7.8E+12 vg/kg
3.9E+13 vg/kg
7.8E+13 vg/kg

FIG. 9H

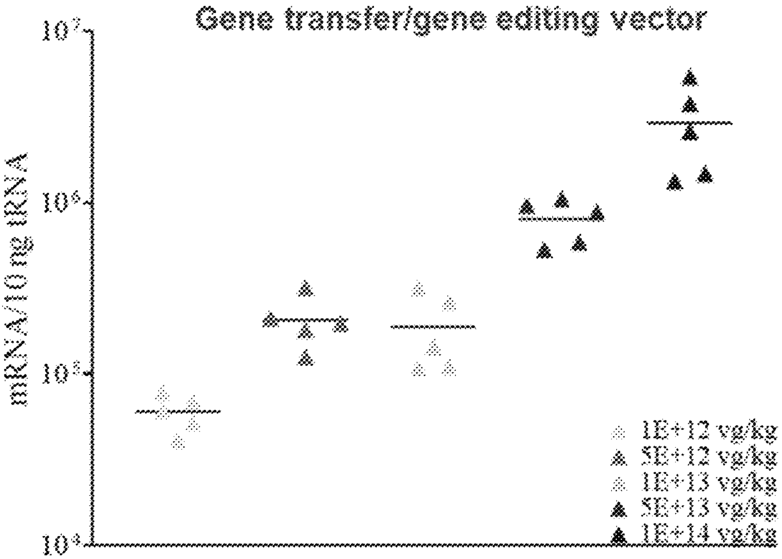

Gene transfer/gene editing vector
mRNA/10 ng tRNA
10^7
10^6
10^5
10^4
1E+12 vg/kg
5E+12 vg/kg
1E+13 vg/kg
5E+13 vg/kg
1E+14 vg/kg

FIG. 9I

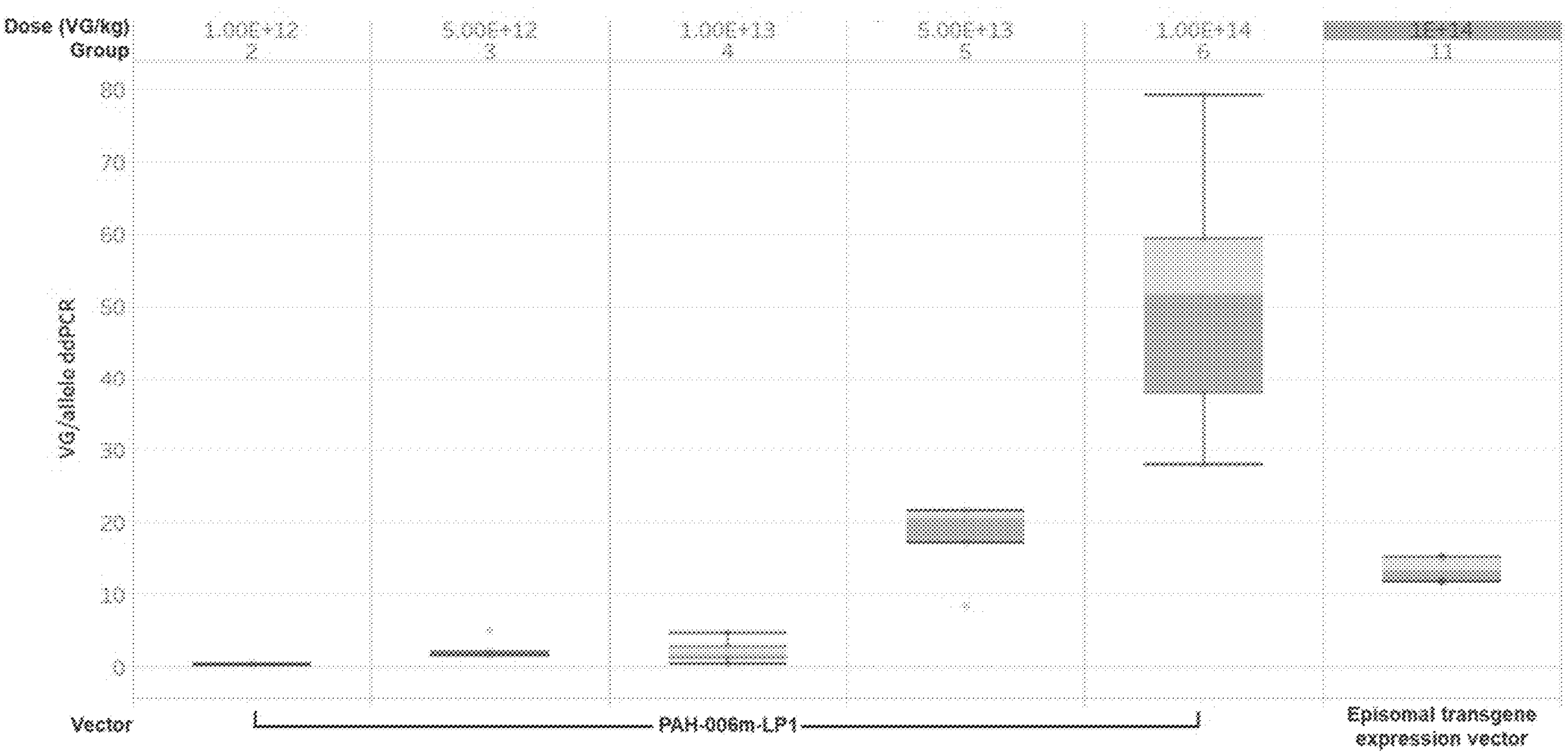

Dose (VG/kg)
Group
1.00E+12
2
5.00E+12
3
1.00E+13
4
5.00E+13
5
1.00E+14
6
1E+13
11
VG/allele ddPCR
80
70
60
50
40
30
20
10
0
Vector
PAH-006m-LP1
Episomal transgene expression vector

FIG. 9J

ON-Target Integration

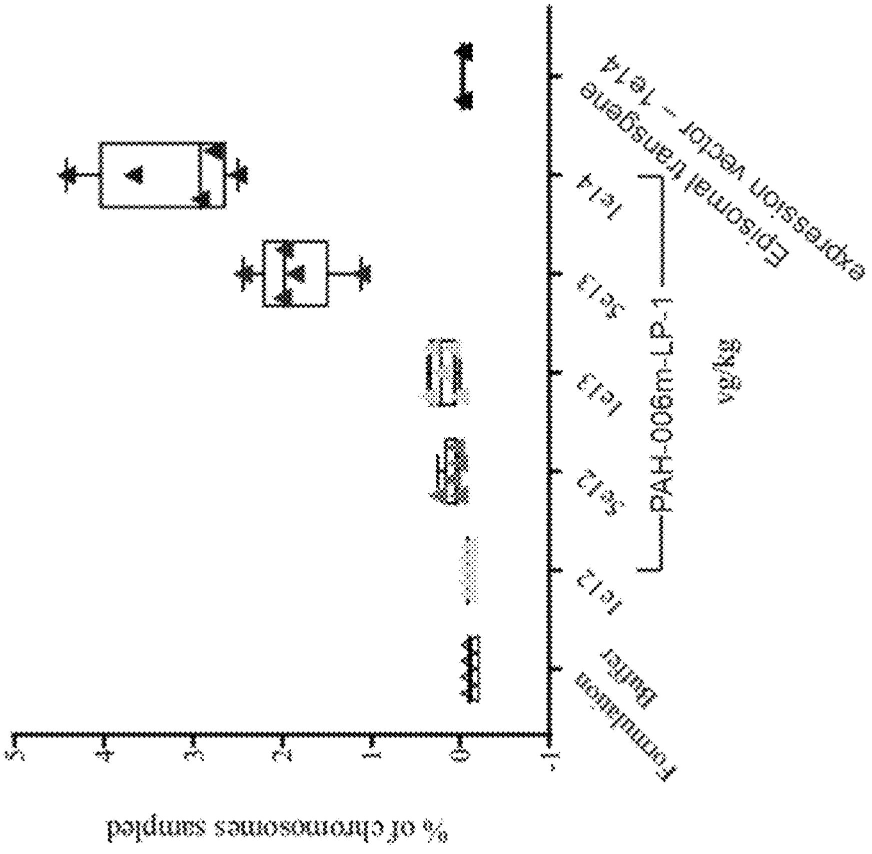


FIG. 9K

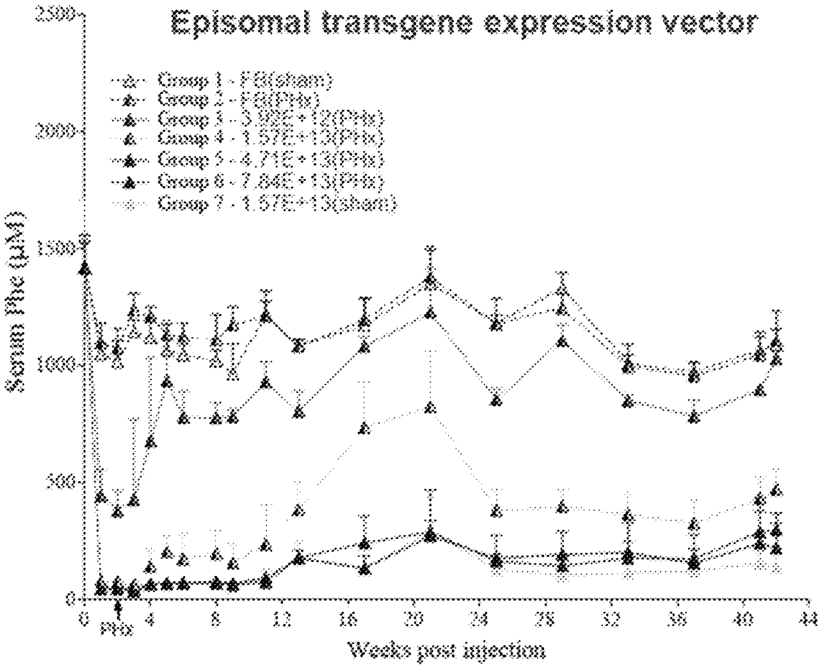

Episomal transgene expression vector
Group 1 - FB(sham)
Group 2 - FB(PHx)
Group 3 - 3.92E+12(PHx)
Group 4 - 1.57E+13(PHx)
Group 5 - 4.71E+13(PHx)
Group 6 - 7.84E+13(PHx)
Group 7 - 1.57E+13(sham)
Serum Phe (μM)
2500
2000
1500
1000
500
0
0
PHx
4
8
12
16
20
24
28
32
36
40
44
Weeks post injection

FIG. 9L

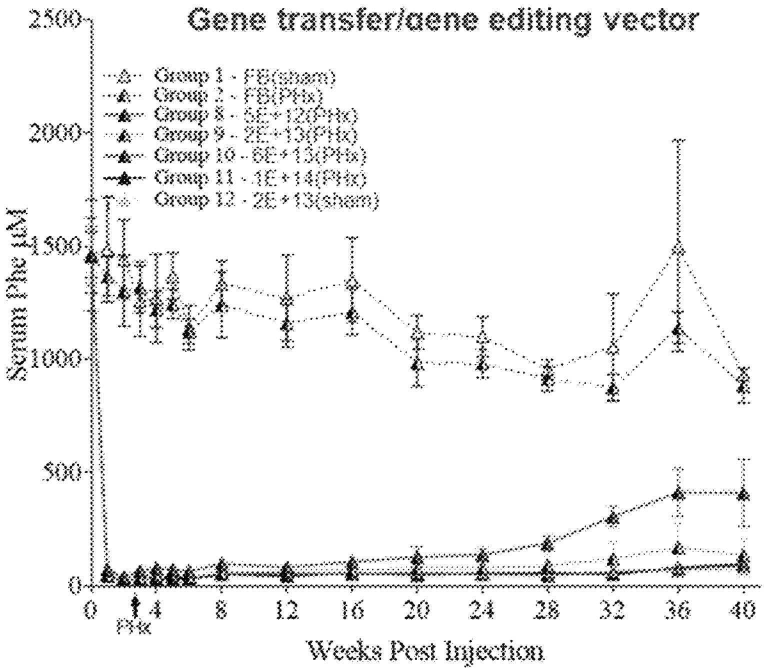

Gene transfer/gene editing vector
Group 1 - FB(sham)
Group 2 - FB(PHx)
Group 8 - 5E+12(PHx)
Group 9 - 2E+13(PHx)
Group 10 - 6E+13(PHx)
Group 11 - 1E+14(PHx)
Group 12 - 2E+13(sham)
Serum Phe μM
2500
2000
1500
1000
500
0
0
PHx
4
8
12
16
20
24
28
32
36
40
Weeks Post Injection

FIG. 10A

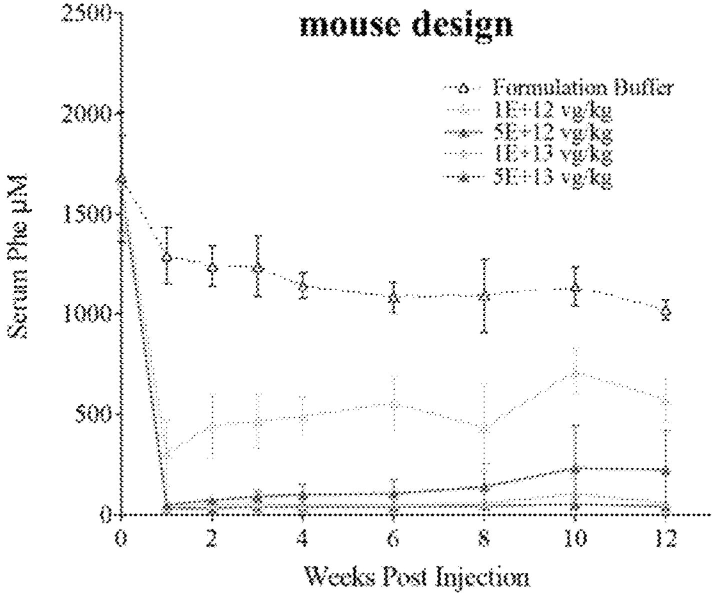


FIG. 10B

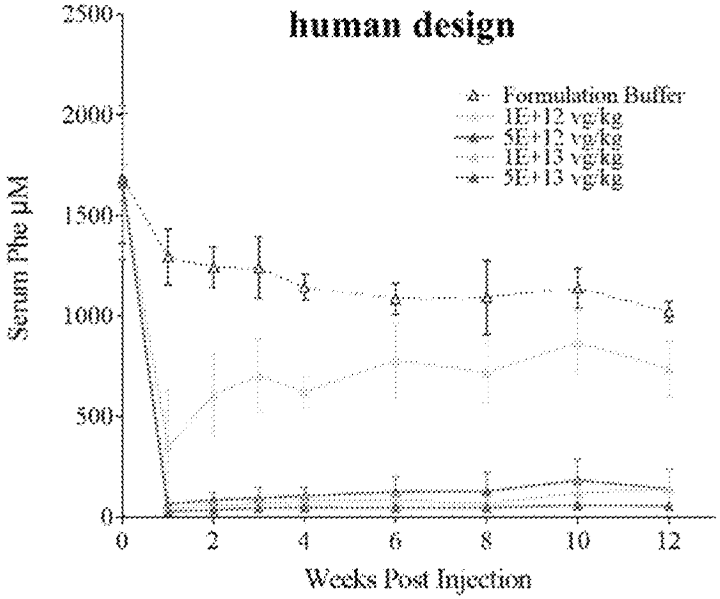
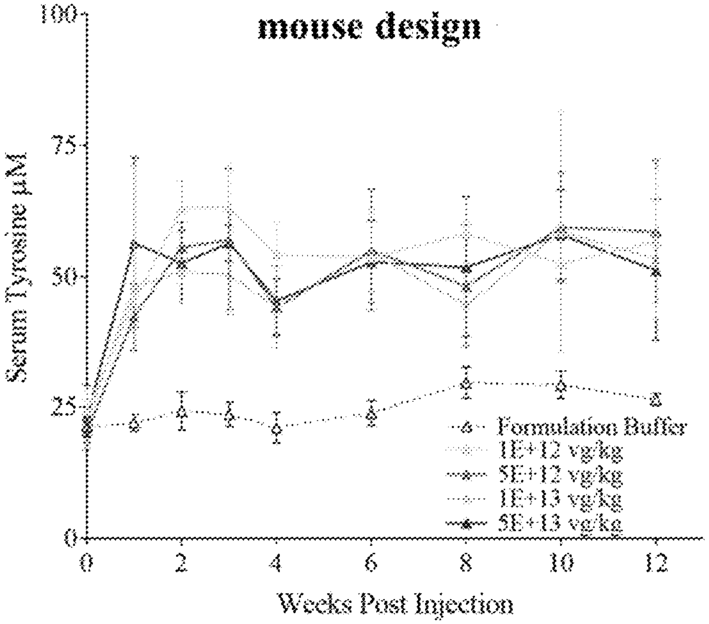
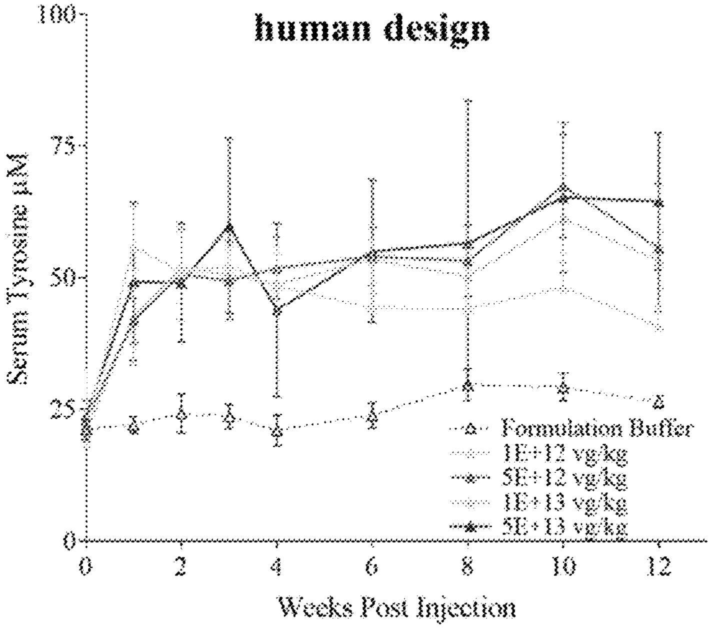


FIG. 10C



mouse design

FIG. 10D



human design

FIG. 10E

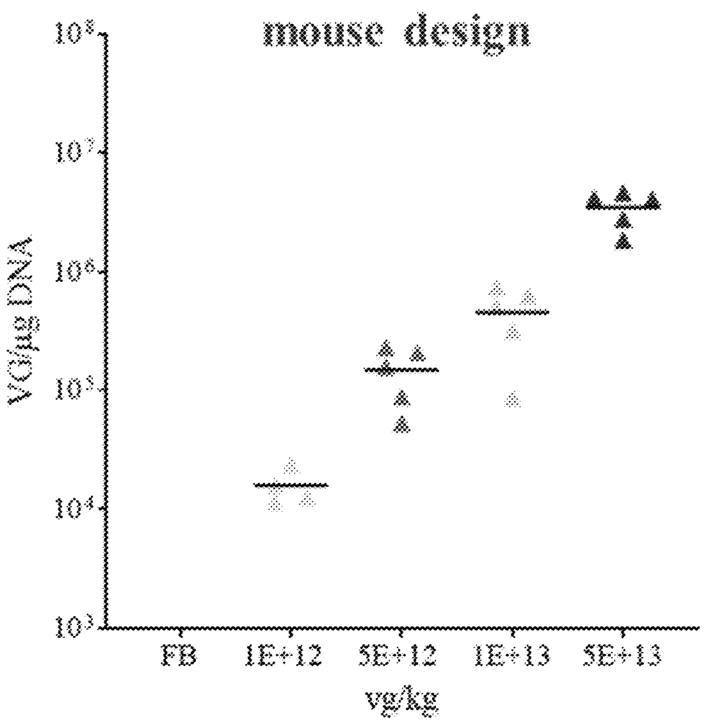


FIG. 10F

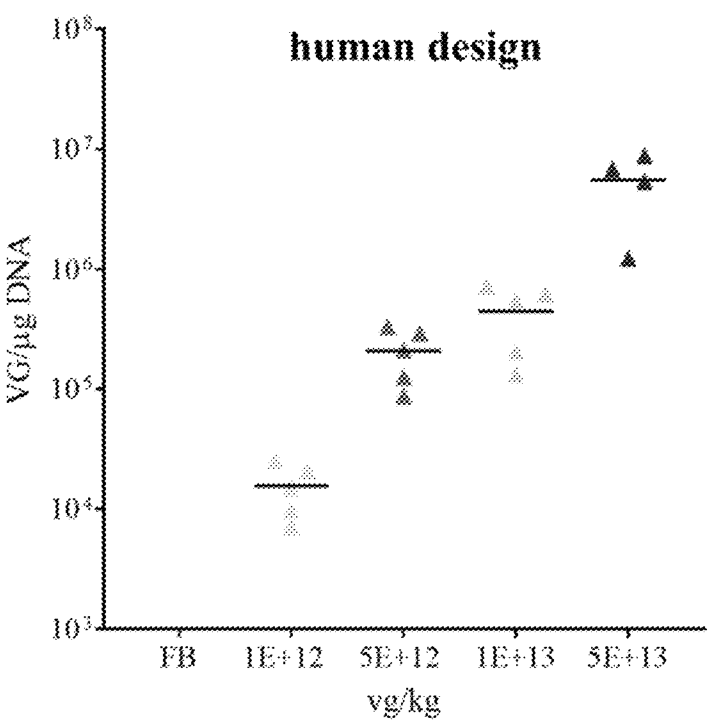


FIG. 10G

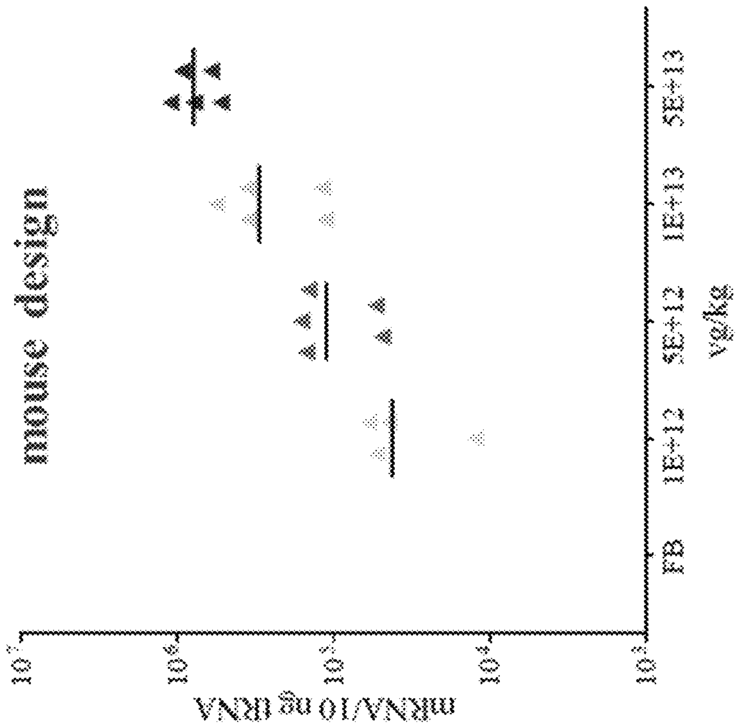


FIG. 10H

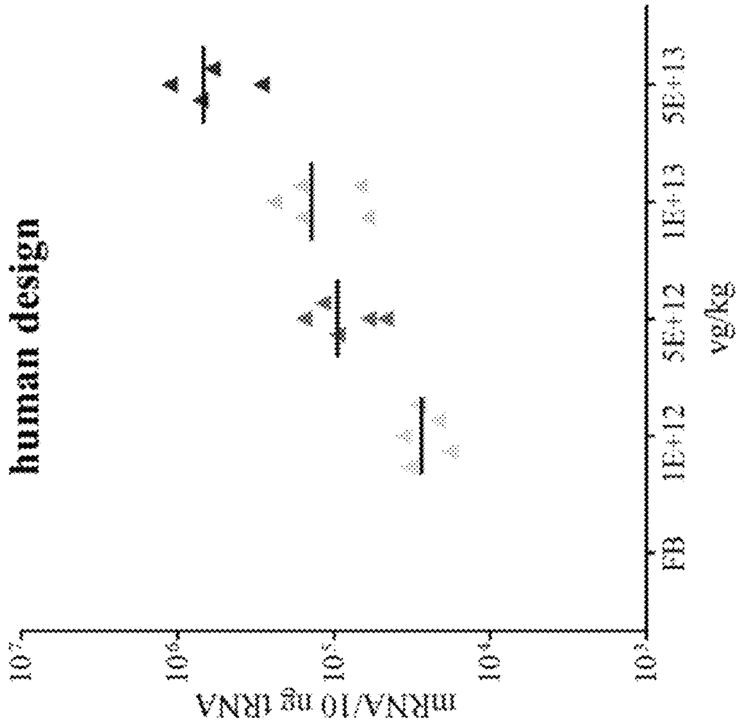


FIG. 10I

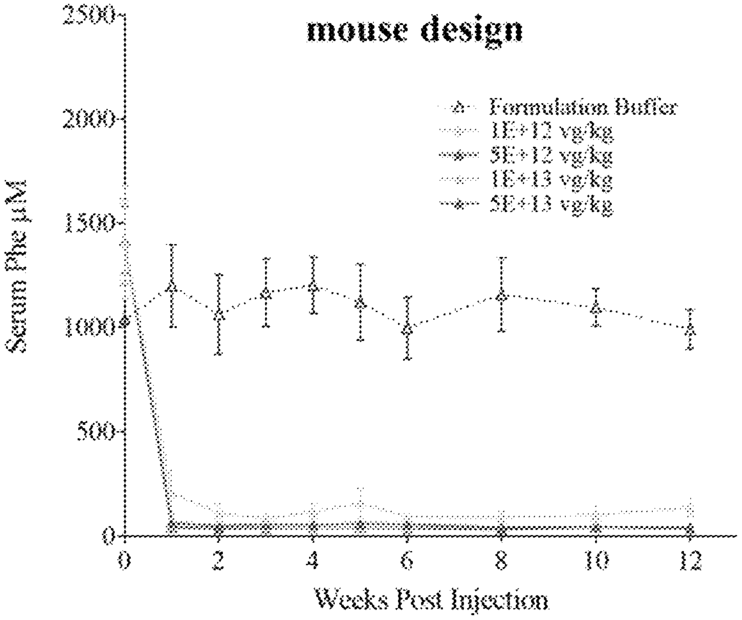


FIG. 10J

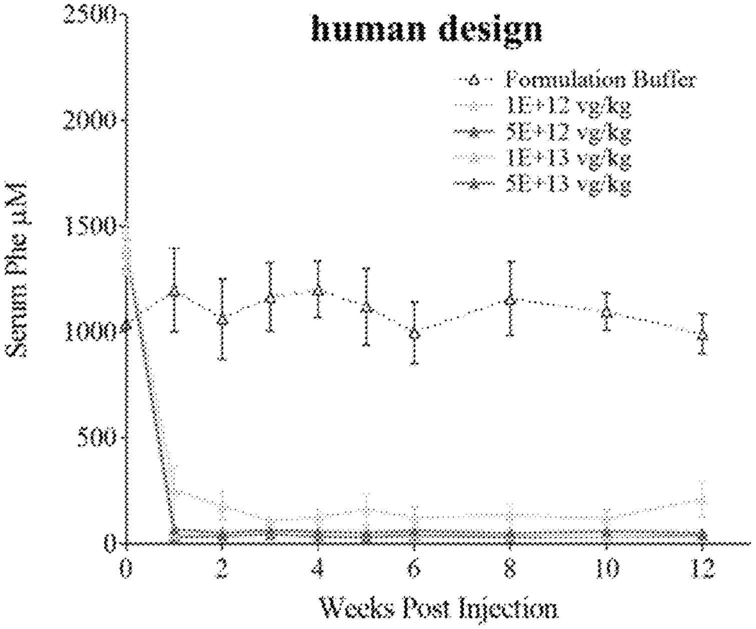
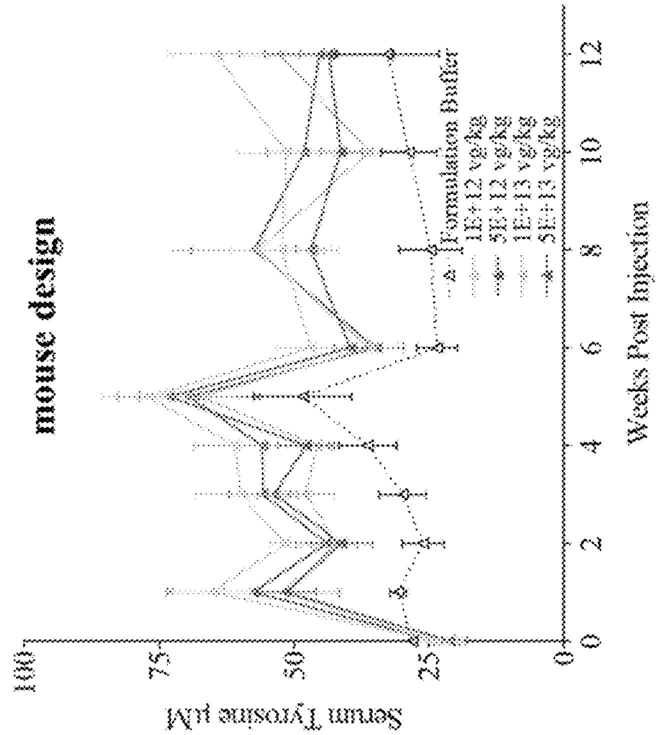
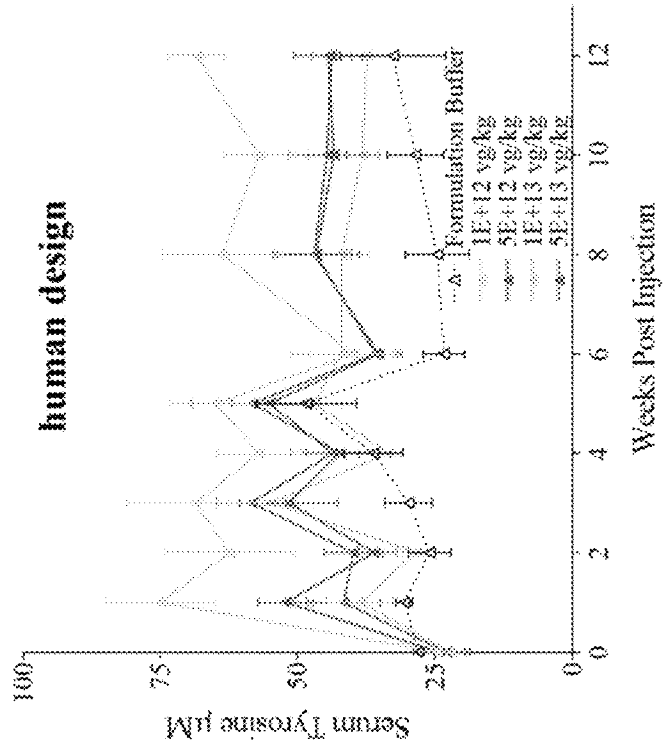


FIG. 10K



mouse design

FIG. 10L



human design

FIG. 10N

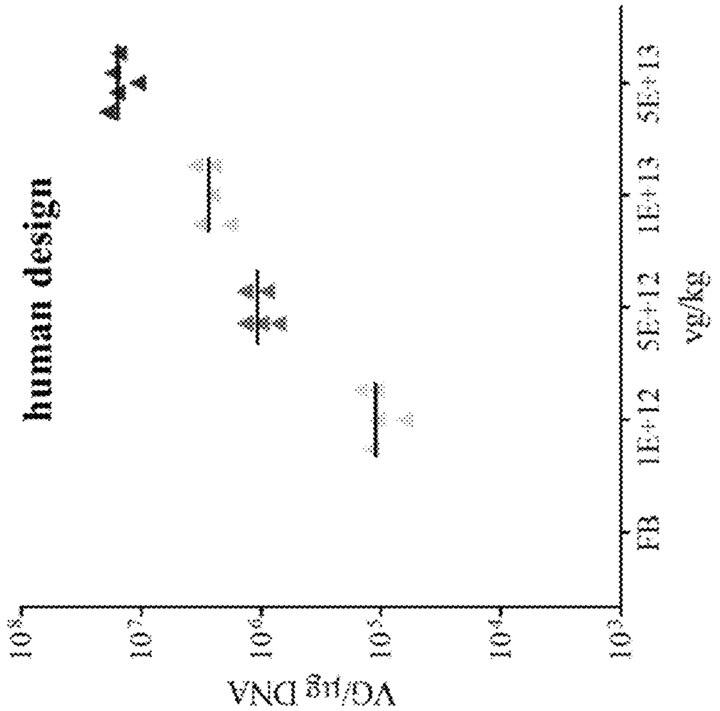


FIG. 10M

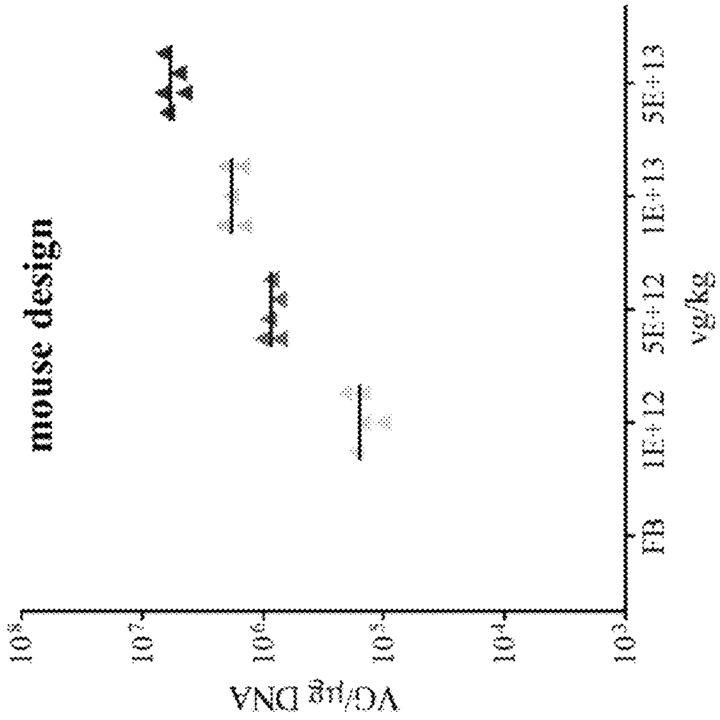


FIG. 10O

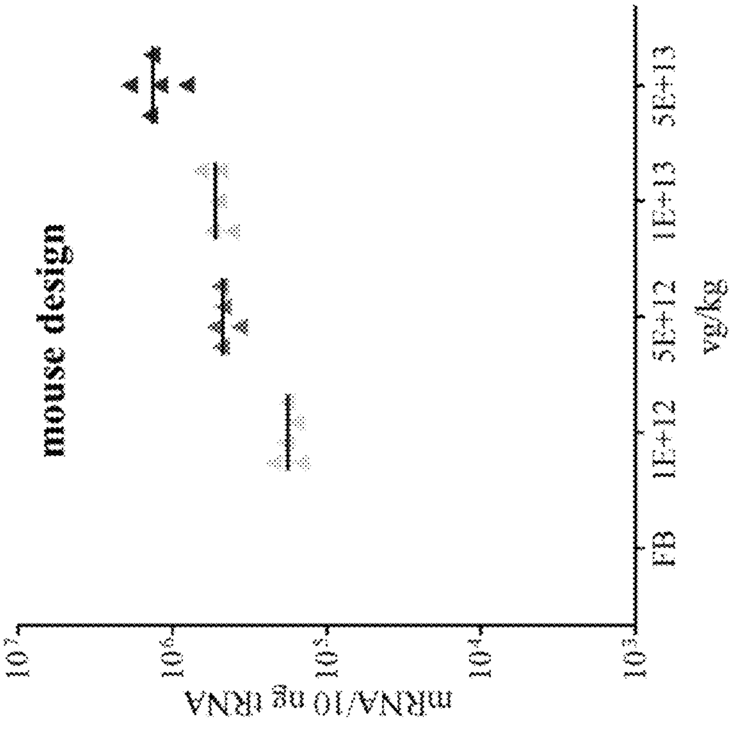


FIG. 10P

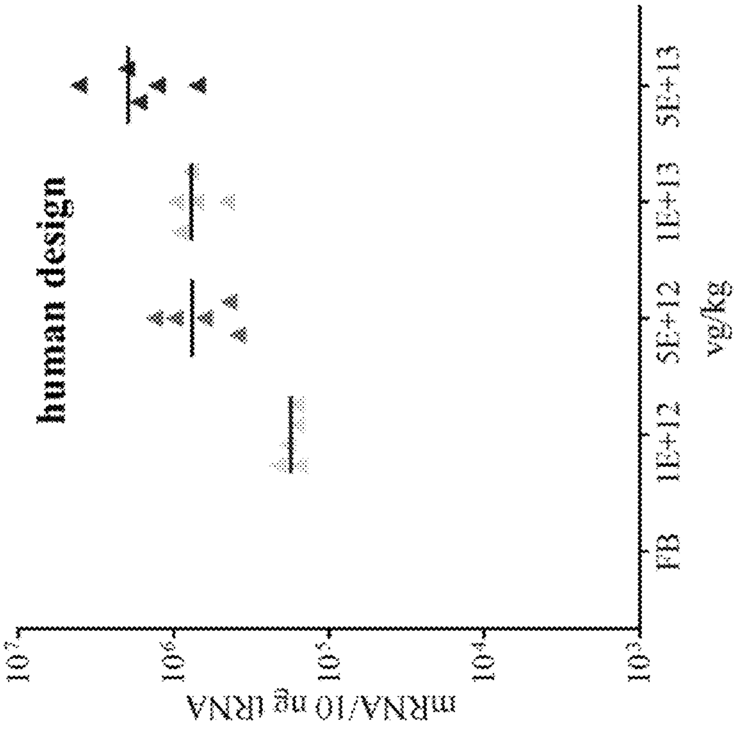


FIG. 11A

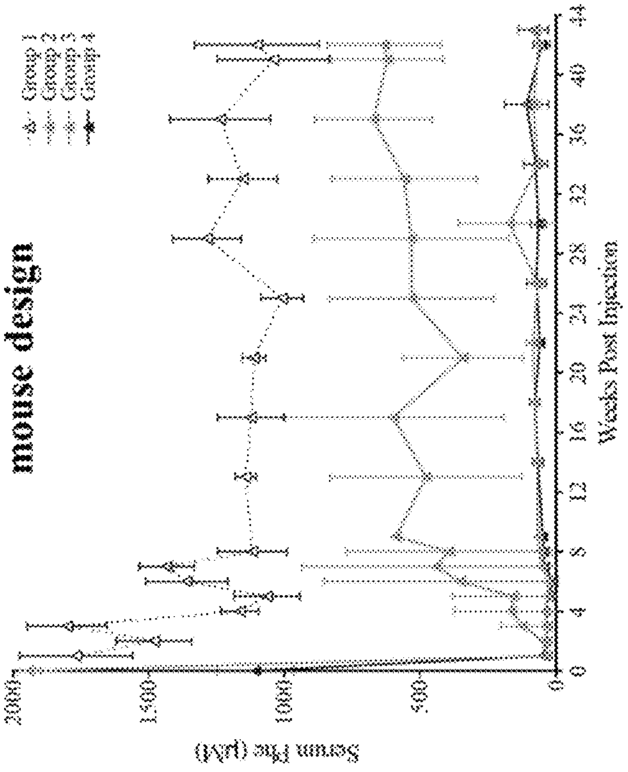

mouse design

FIG. 11B

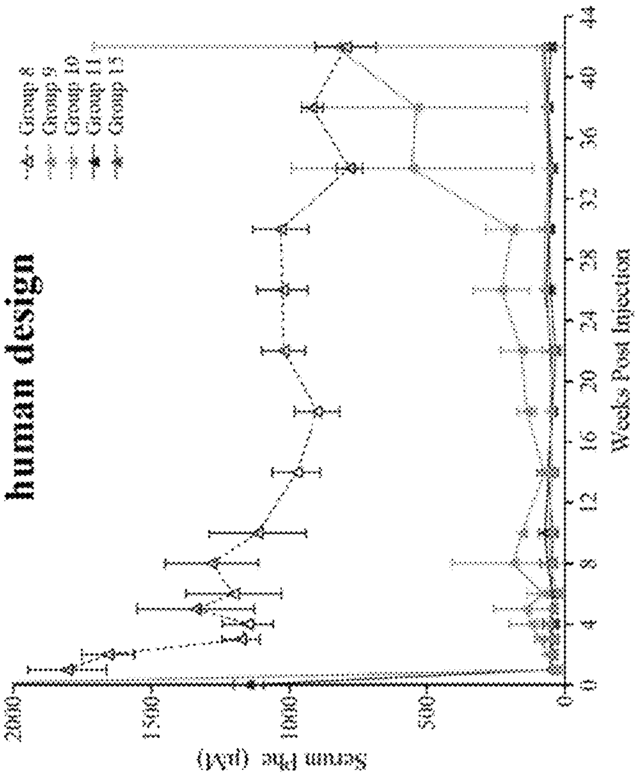
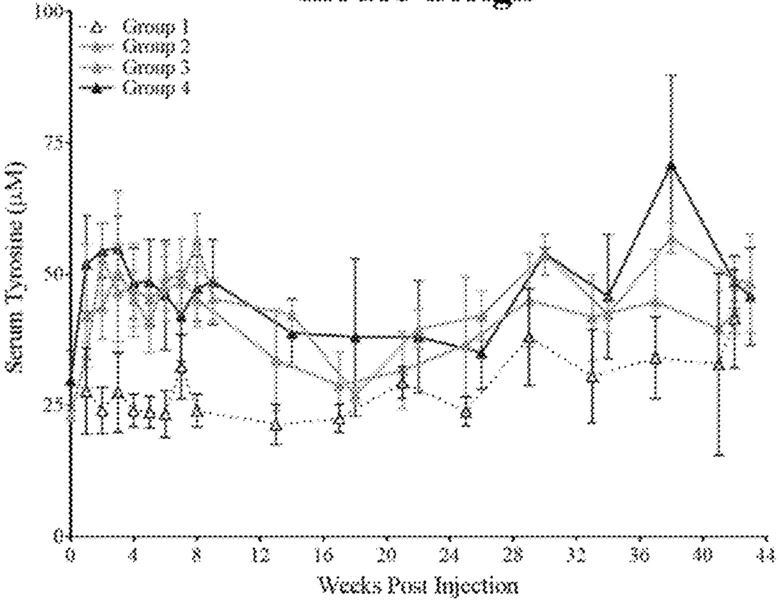
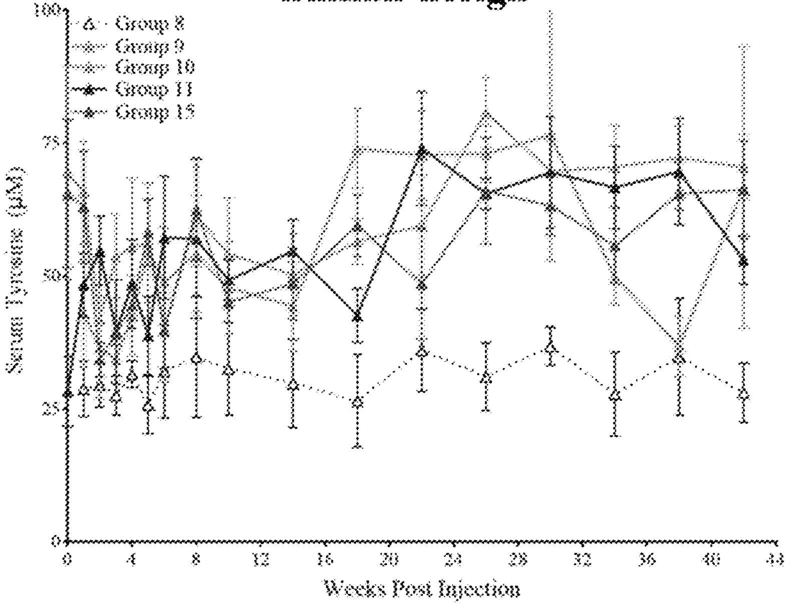

human design

FIG. 11C



mouse design

FIG. 11D



human design

FIG. 11E

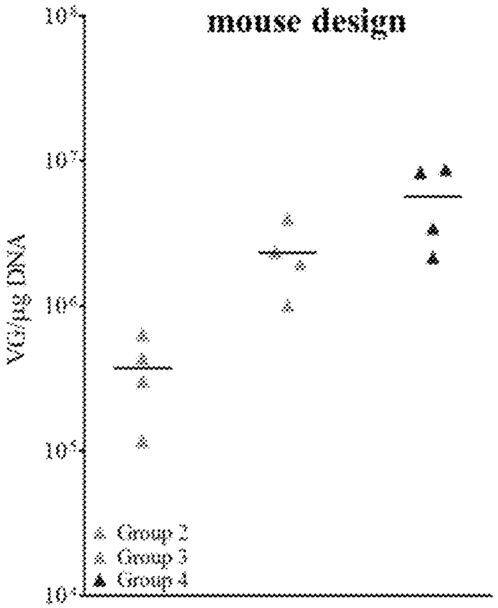


FIG. 11F

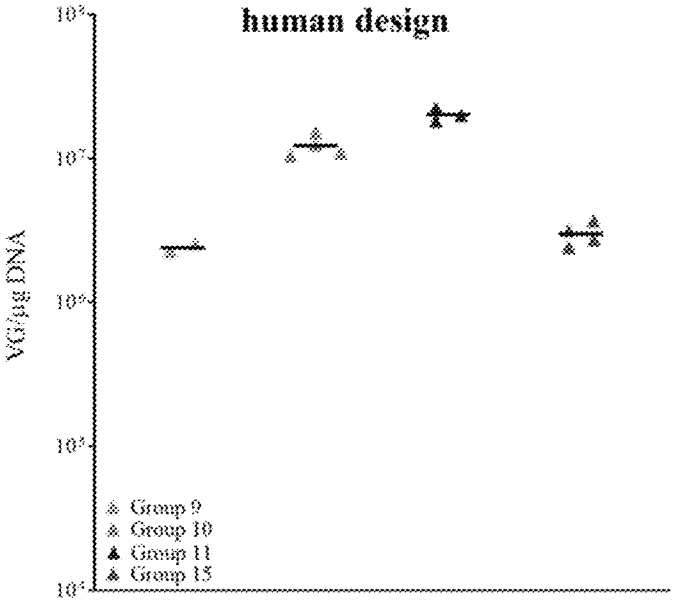


FIG. 11G

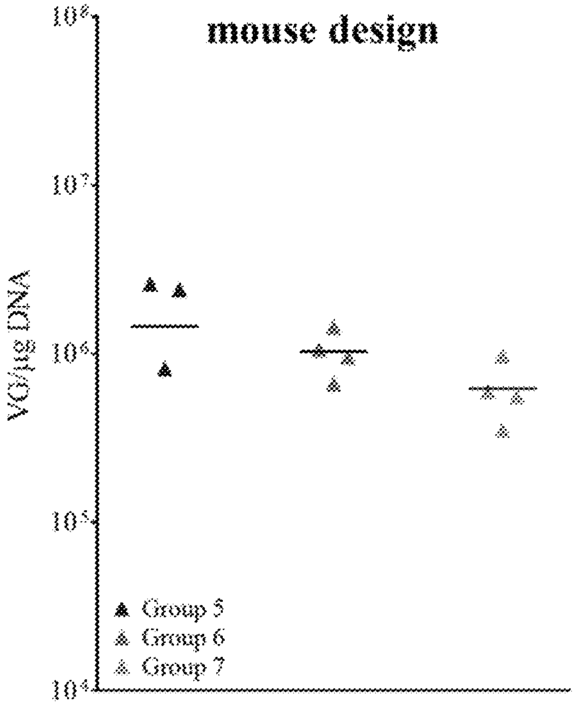


FIG. 11H

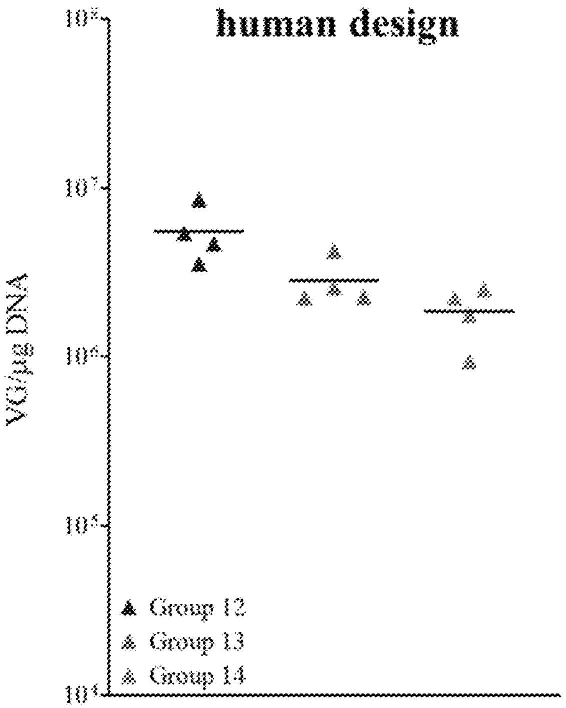


FIG. 11I

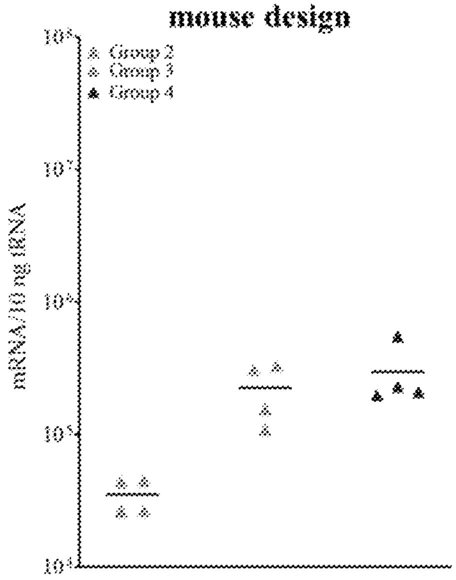


FIG. 11J

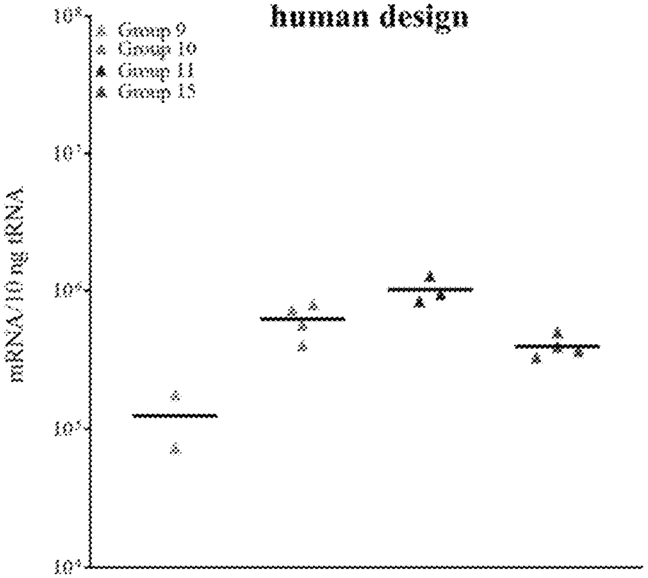


FIG. 11K

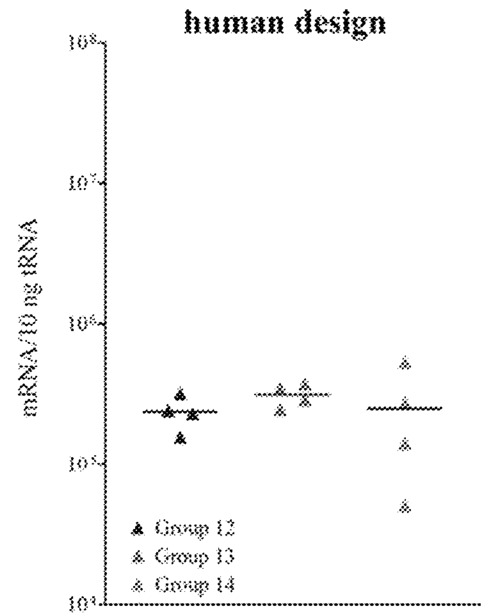

human design

FIG. 12A

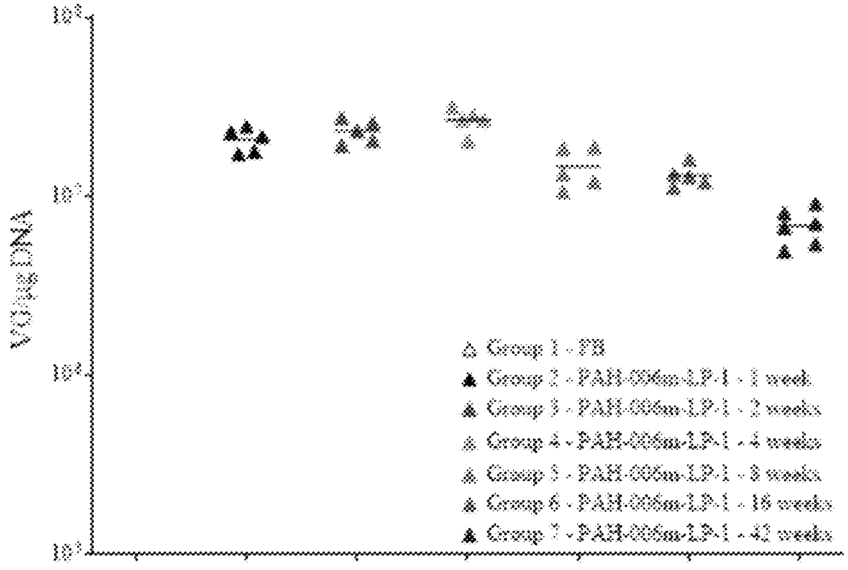


FIG. 12B

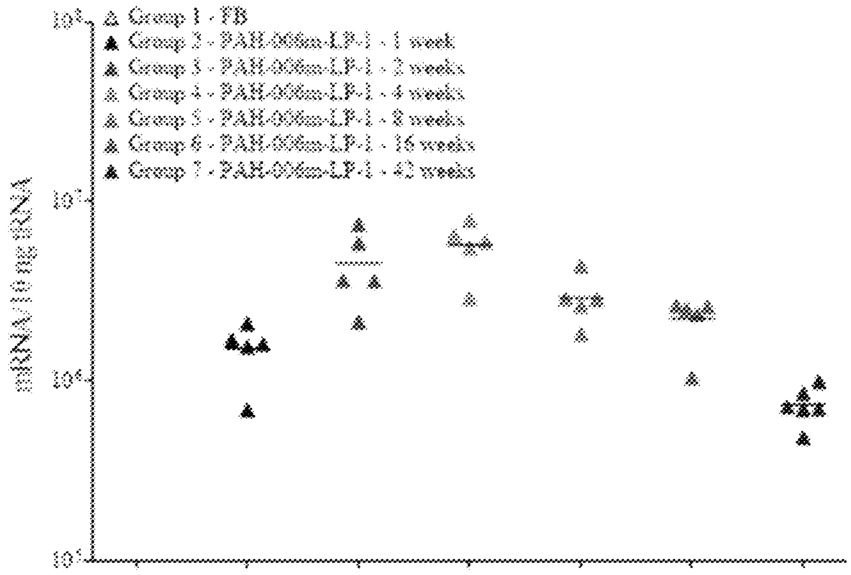


FIG. 12C

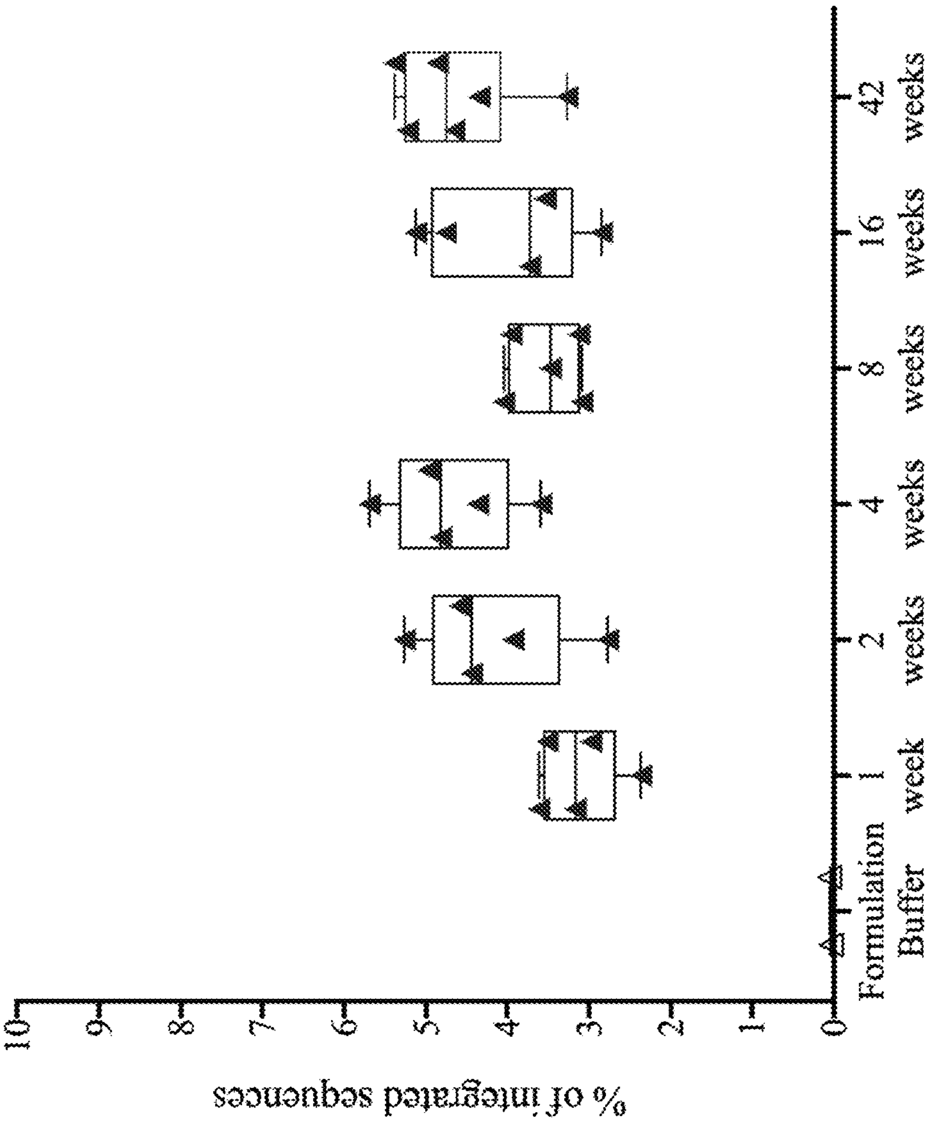

% of integrated sequences
0
1
2
3
4
5
6
7
8
9
10
Formulation Buffer
1 week
2 weeks
4 weeks
8 weeks
16 weeks
42 weeks

FIG. 12D

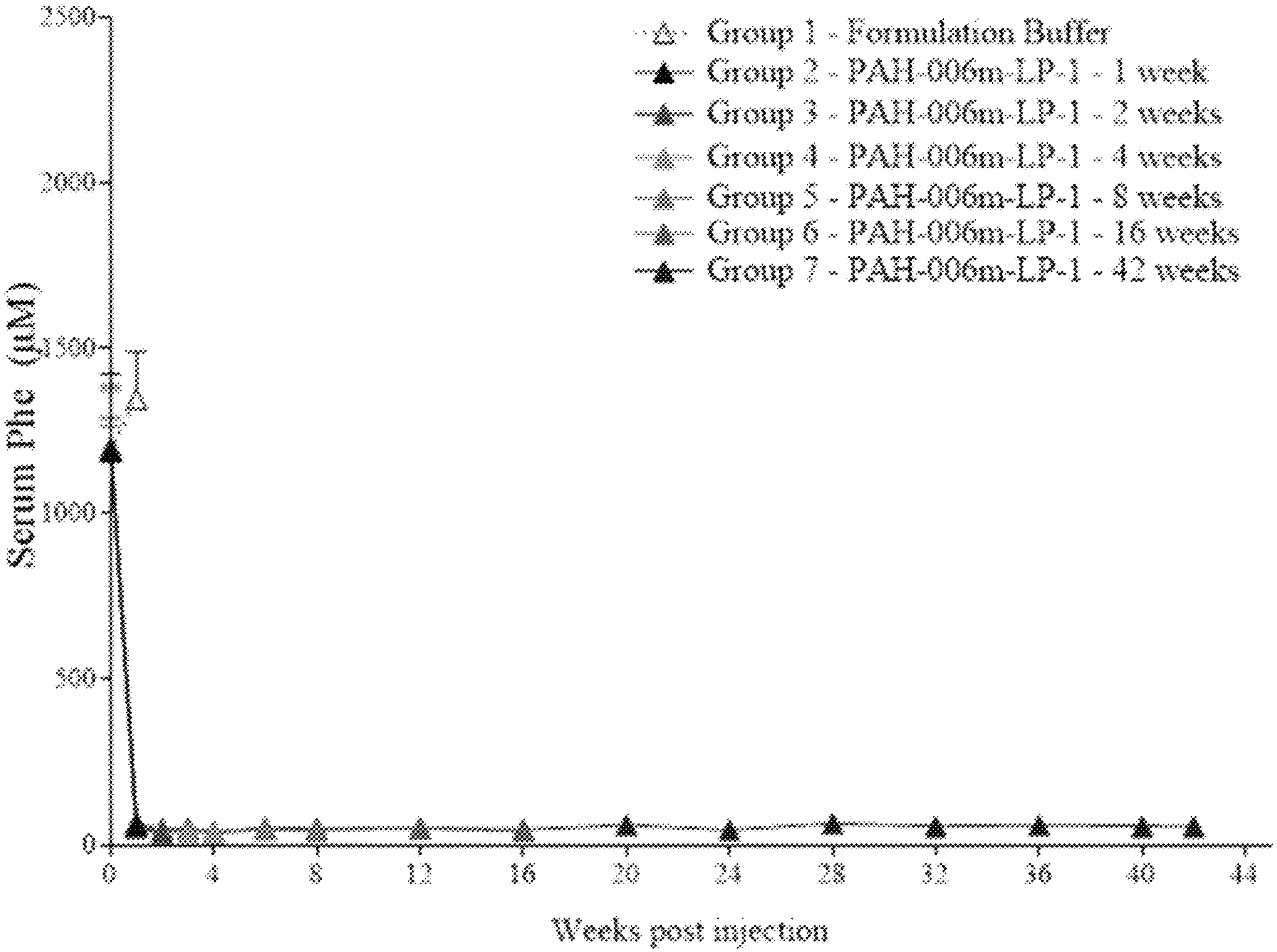

Group 1 - Formulation Buffer
Group 2 - PAH-006m-LP-1 - 1 week
Group 3 - PAH-006m-LP-1 - 2 weeks
Group 4 - PAH-006m-LP-1 - 4 weeks
Group 5 - PAH-006m-LP-1 - 8 weeks
Group 6 - PAH-006m-LP-1 - 16 weeks
Group 7 - PAH-006m-LP-1 - 42 weeks
Serum Phe (µM)
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
28
32
36
40
44
Weeks post injection

FIG. 12E

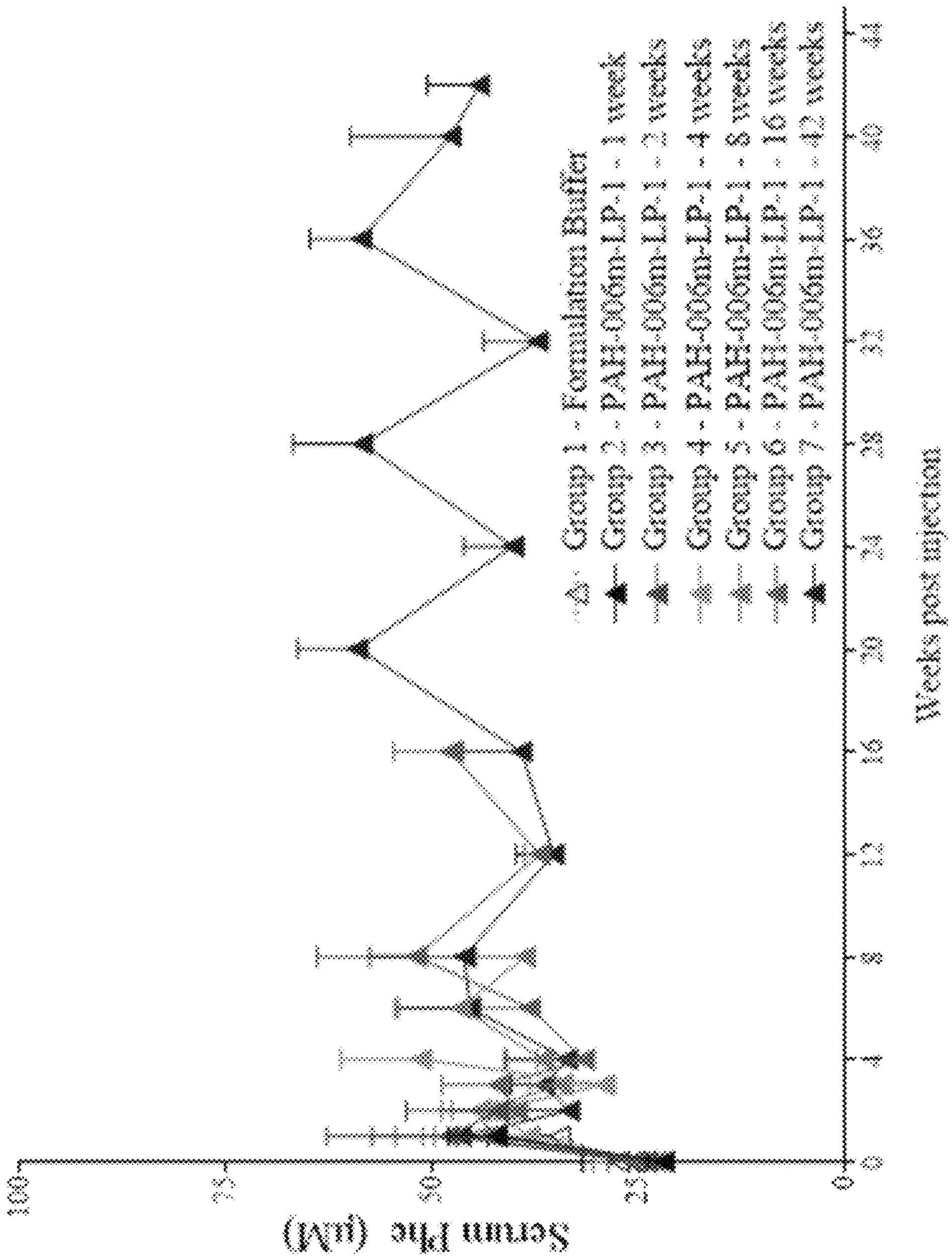

Serum Phe (µM)
100
75
50
25
0
0
4
8
12
16
20
24
28
32
36
40
44
Weeks post injection
Group 1 - Formulation Buffer
Group 2 - PAH-006m-LP-1 - 1 week
Group 3 - PAH-006m-LP-1 - 2 weeks
Group 4 - PAH-006m-LP-1 - 4 weeks
Group 5 - PAH-006m-LP-1 - 8 weeks
Group 6 - PAH-006m-LP-1 - 16 weeks
Group 7 - PAH-006m-LP-1 - 42 weeks

FIG. 13A

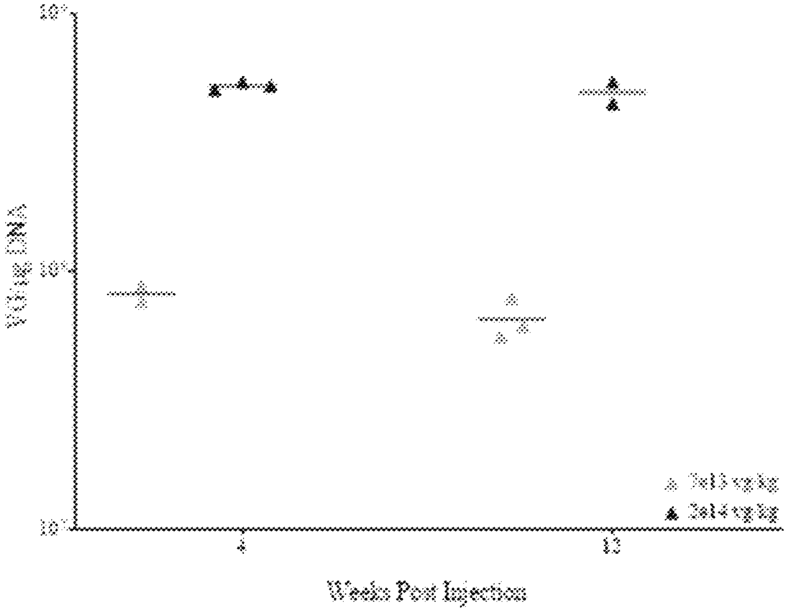


FIG. 13B

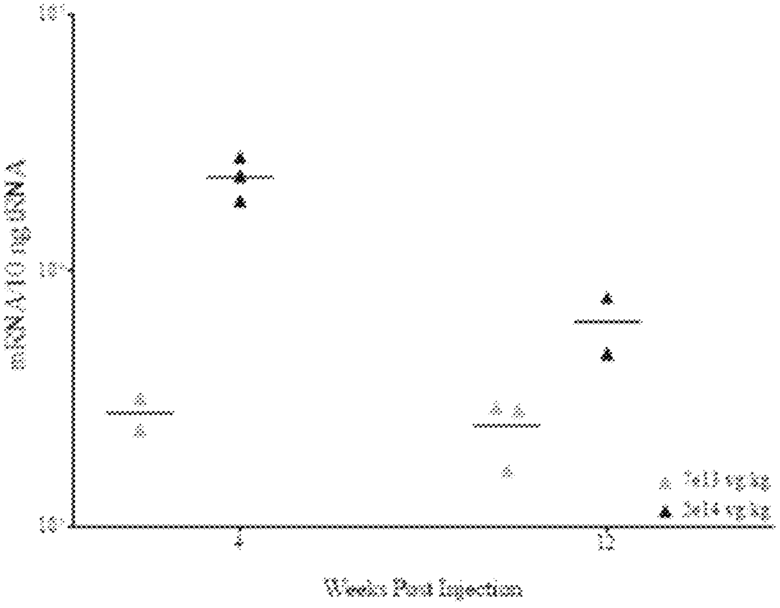


FIG. 13C

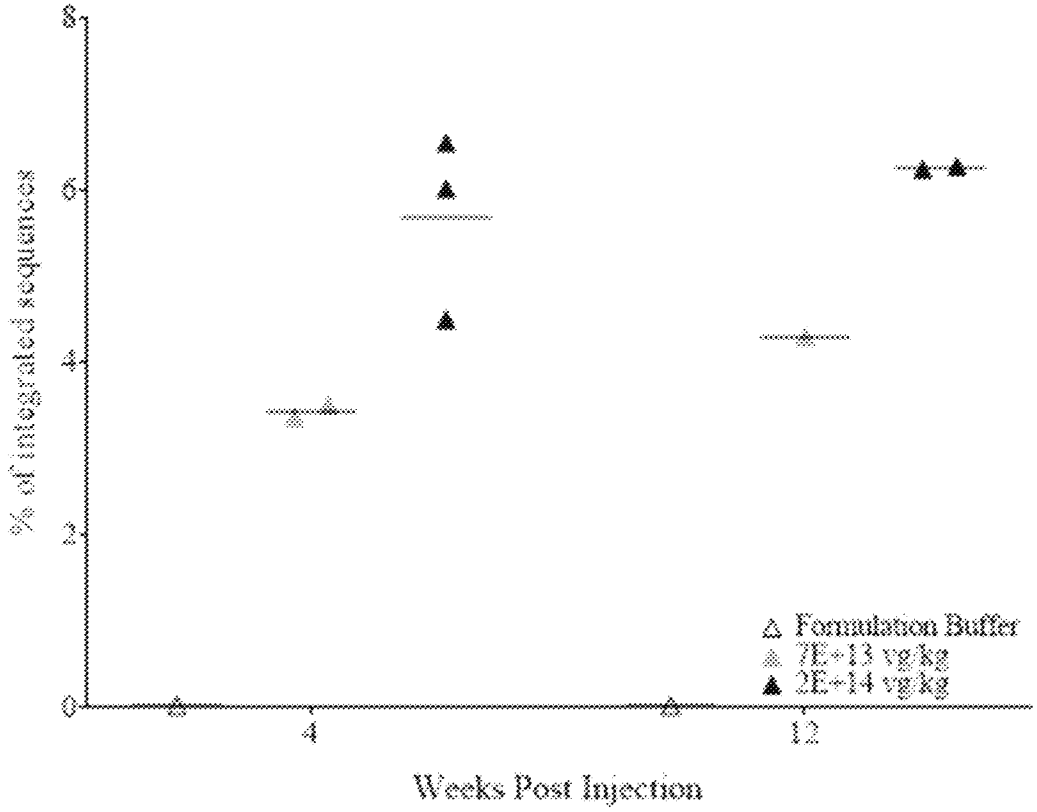

% of integrated sequences
8
6
4
2
0
4
12
Weeks Post Injection
△ Formulation Buffer
▲ 7E+13 vg/kg
▲ 2E+14 vg/kg

FIG. 14A

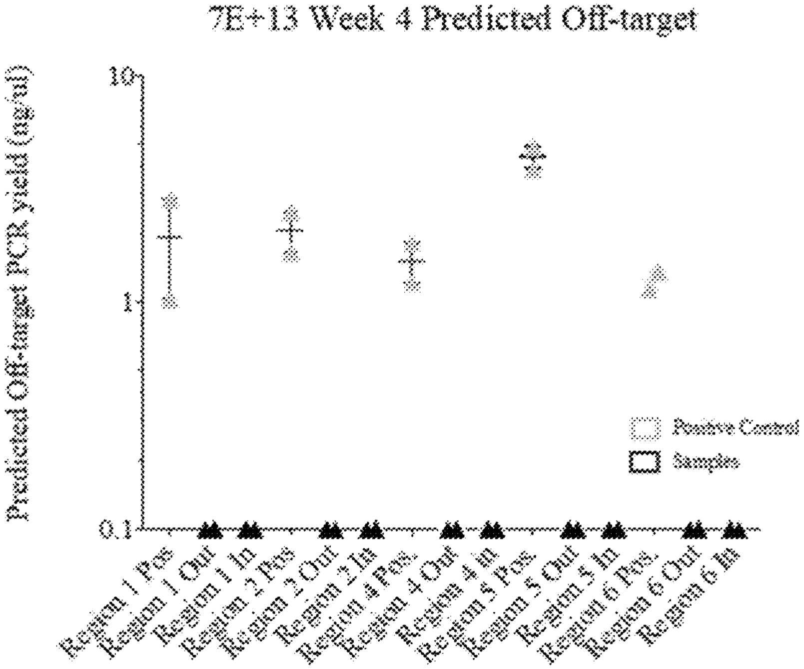


FIG. 14B

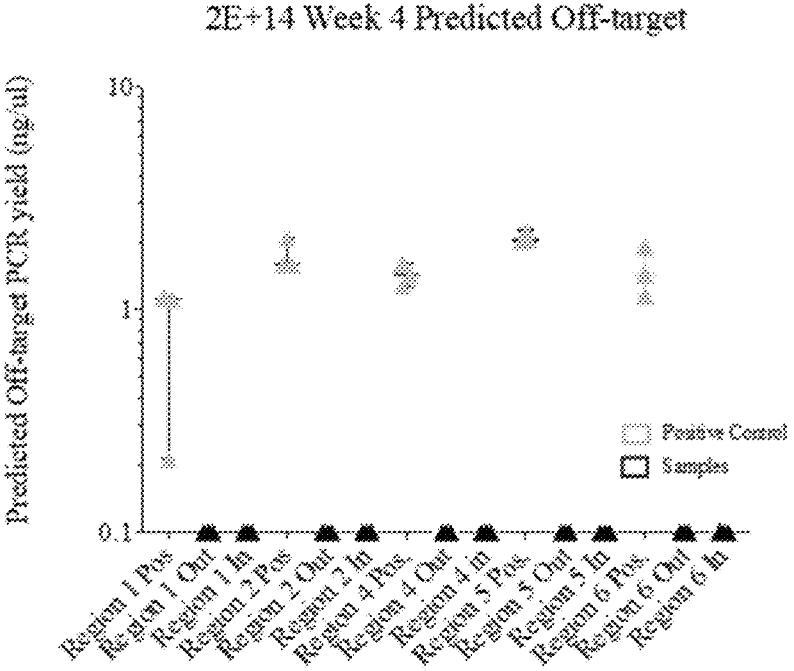


FIG. 14C

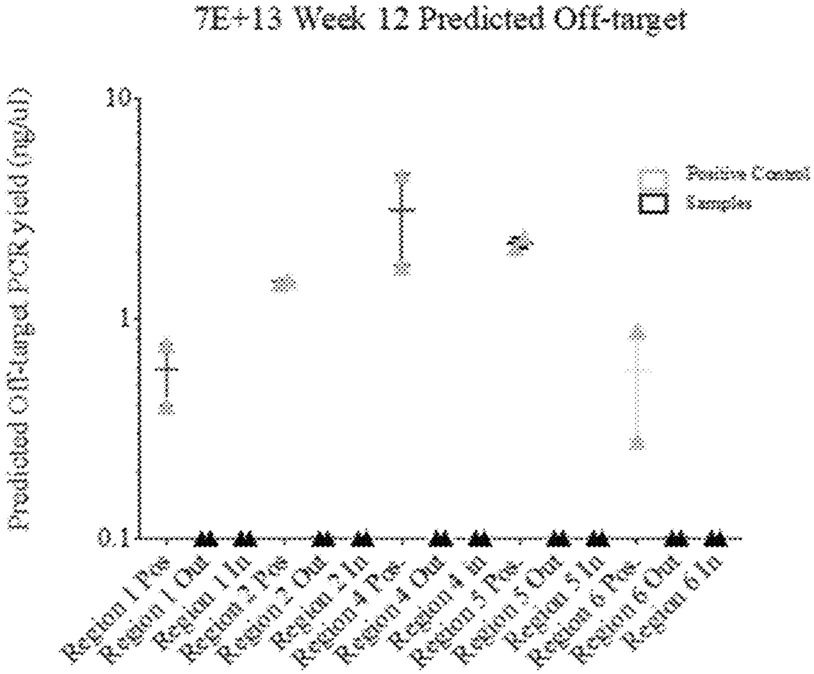
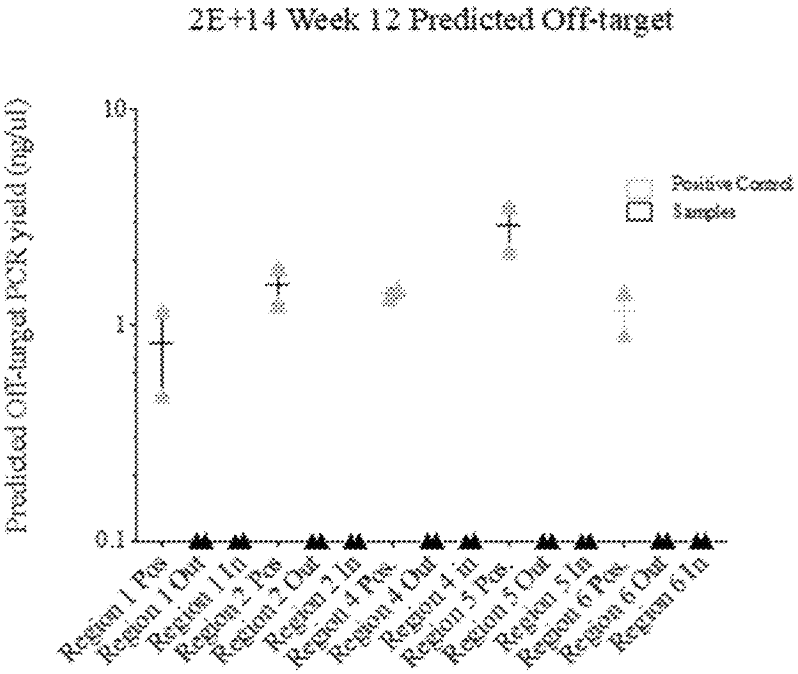

7E+13 Week 12 Predicted Off-target

FIG. 14D


2E+14 Week 12 Predicted Off-target

ADENO-ASSOCIATED VIRUS COMPOSITIONS FOR RESTORING PAH GENE FUNCTION AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial Nos. 63/030,341, filed May 27, 2020, and 63/117,252, filed Nov. 23, 2020, the entire disclosures of which are hereby incorporated herein by reference.

SEQUENCE LISTING

This application contains a sequence listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety (said ASCII copy, created on May 24, 2021, is named "404217-HMW-040US-183160_SL.txt" and is 213,352 bytes in size).

BACKGROUND

Phenylketonuria (PKU) is an autosomal recessive genetic disorder where the majority of cases are caused by mutations in the phenylalanine hydroxylase (PAH) gene. The PAH gene encodes a hepatic enzyme that catalyzes the hydroxylation of L-phenylalanine (Phe) to L-tyrosine (Tyr) upon multimerization. Reduction or loss of PAH activity leads to phenylalanine accumulation and its conversion into phenylpyruvate (also known as phenylketone). This abnormality in phenylalanine metabolism impairs neuronal maturation and the synthesis of myelin, resulting in mental retardation, seizures, and other serious medical problems.

Currently, there is no cure for PKU. The standard of care is diet management by minimizing foods that contain high amounts of phenylalanine. Dietary management from birth with a low phenylalanine formula largely prevents the development of the neurological consequences of the disorder. However, even on a low-protein diet, children still suffer from growth retardation, and adults often have osteoporosis and vitamin deficiencies. Moreover, adherence to life-long dietary treatment is difficult, particularly beyond school age.

New treatment strategies have recently emerged, including large neutral amino acid (LNAA) supplementation, cofactor tetrahydrobiopterin therapy, enzyme replacement therapy, and genetically modified probiotic therapy. However, these strategies suffer from shortcomings. The LNAA supplementation is suitable only for adults not adhering to a low Phe diet. The cofactor tetrahydrobiopterin can only be used in some mild forms of PKU. Enzyme replacement by administration of a substitute for PAH, e.g., phenylalanine ammonia-lyase (PAL), can lead to immune responses that reduce the efficacy and/or cause side effects. As to genetically modified probiotic therapy, the pathogenicity of PAL-expressing *E. coli* has been a concern.

Gene therapy provides a unique opportunity to cure PKU. Retroviral vectors, including lentiviral vectors, are capable of integrating nucleic acids into host cell genomes. However, these vectors may raise safety concerns due to their non-targeted insertion into the genome. For example, there is a risk of the vector disrupting a tumor suppressor gene or activating an oncogene, thereby causing a malignancy. Indeed, in a clinical trial for treating X-linked severe combined immunodeficiency (SCID) by transducing $CD34^+$ bone marrow precursors with a gammaretroviral vector, four out of ten patients developed leukemia (Hacein-Bey-Abina et al. *J Clin Invest.* (2008) 118(9):3132-42).

It has also been speculated that nuclease-based gene editing technologies, such as meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered, regularly interspaced, short palindromic repeat (CRISPR) technology, may be used to correct defects in the PAH gene in PKU patients. However, each of these technologies raises safety concerns due to the potential for off-target mutation of sites in the human genome similar in sequence to the intended target site.

Accordingly, there is a need in the art for improved gene therapy compositions and methods that can efficiently and safely restore PAH gene function in PKU patients.

SUMMARY

Provided herein are recombinant adeno-associated virus (rAAV) compositions that can restore PAH gene function in cells, and methods for using the same to treat diseases associated with reduction of PAH gene function (e.g., PKU). Also provided are nucleic acids, vectors, packaging systems, and methods for making the adeno-associated virus compositions. The rAAV compositions provided herein are particularly advantageous in that they can efficiently edit the genome of cells (e.g., liver cells) in a subject to express PAH under the control of a liver-specific promoter, and thereby offer a potential cure for PKU patients.

Accordingly, in one aspect, the instant disclosure provides a recombinant adeno-associated virus (rAAV) comprising: (a) an AAV capsid comprising an AAV capsid protein; and (b) an rAAV genome comprising: (i) an editing element for editing a target locus in a PAH gene, comprising at least a portion of a PAH coding sequence operably linked to a transcriptional regulatory element; (ii) a 5' homology arm nucleotide sequence position 5' of the editing element, having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence positioned 3' of the editing element, having homology to a second genomic region 3' to the target locus.

In certain embodiments, the editing element comprises a PAH coding sequence. In certain embodiments, the PAH coding sequence encodes an amino acid sequence set forth in SEQ ID NO: 33. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 53. In certain embodiments, the PAH coding sequence is silently altered. In certain embodiments, the PAH coding sequence comprises a nucleotide sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the nucleotide sequence set forth in SEQ ID NO: 28, 63, or 83. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 63. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 83.

In certain embodiments, the transcriptional regulatory element is capable of mediating transcription in a hepatocyte, a renal cell, or a cell in the brain, pituitary gland, adrenal gland, pancreas, urinary bladder, gallbladder, colon, small intestine, or breast. In certain embodiments, the transcriptional regulatory element is endogenous to the PAH gene. In certain embodiments, the transcriptional regulatory element is exogenous to the PAH gene. In certain embodiments, the transcriptional regulatory element is liver specific, optionally wherein the transcriptional regulatory element comprises one or more elements selected from the group consisting of a human albumin promoter, a human transthyretin (TTR) promoter, a human ApoE/C-I hepatic control region (HCR) 1 or 2, a human ApoH promoter, a human SERPINA1 (hAAT) promoter, and a hepatic specific regulatory module thereof. In certain embodiments, the transcriptional regulatory element comprises a nucleotide sequence at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 25, 26, 27, or 69. In certain embodiments, the transcriptional regulatory element comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 27. In certain embodiments, the transcriptional regulatory element comprises the nucleotide sequence set forth in SEQ ID NO: 27. In certain embodiments, the transcriptional regulatory element consists of the nucleotide sequence set forth in SEQ ID NO: 27.

In certain embodiments, the editing element further comprises an intron element positioned 5' to the PAH coding sequence and 3' to the transcriptional regulatory element. In certain embodiments, the intron element is an exogenous intron element, optionally wherein the exogenous intron element is an SV40 intron element. In certain embodiments, the SV40 intron element comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 29. In certain embodiments, the SV40 intron element comprises the nucleotide sequence set forth in SEQ ID NO: 29. In certain embodiments, the SV40 intron element consists of the nucleotide sequence set forth in SEQ ID NO: 29.

In certain embodiments, the editing element further comprises a polyadenylation sequence 3' to the PAH coding sequence. In certain embodiments, the polyadenylation sequence is an exogenous polyadenylation sequence, optionally wherein the exogenous polyadenylation sequence is an SV40 polyadenylation sequence. In certain embodiments, the SV40 polyadenylation sequence comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 31. In certain embodiments, the SV40 polyadenylation sequence comprises the nucleotide sequence set forth in SEQ ID NO: 31. In certain embodiments, the SV40 polyadenylation sequence consists of the nucleotide sequence set forth in SEQ ID NO: 31.

In certain embodiments, the nucleotide 5' to the target locus is in an intron of a PAH gene. In certain embodiments, the nucleotide 5' to the target locus is in intron 1 of a PAH gene. In certain embodiments, the nucleotide 3' to the target locus is in an intron of a PAH gene. In certain embodiments, the nucleotide 3' to the target locus is in intron 1 of a PAH gene.

In certain embodiments, the PAH gene is a human PAH gene. In certain embodiments, the human PAH gene is wild-type. In certain embodiments, the human PAH gene is a variant PAH gene.

In certain embodiments, the editing element comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 25, 26, 27, 28, 29, 31, 50, 51, 52, 69, or 70.

In certain embodiments, the 5' homology arm nucleotide sequence is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the first genomic region. In certain embodiments, the 3' homology arm nucleotide sequence is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the second genomic region. In certain embodiments, the first genomic region is located in a first editing window, and the second genomic region is located in a second editing window. In certain embodiments, the first editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37. In certain embodiments, the second editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38. In certain embodiments, the first genomic region consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37. In certain embodiments, the second genomic region consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38. In certain embodiments, each of the 5' and 3' homology arm nucleotide sequences independently has a length of about 100 to about 2000 nucleotides. In certain embodiments, the 5' homology arm comprises a nucleotide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 23. In certain embodiments, the 5' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 23. In certain embodiments, the nucleotide sequence of the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 23. In certain embodiments, the 3' homology arm comprises a nucleotide sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 24. In certain embodiments, the 3' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 24. In certain embodiments, the nucleotide sequence of the 3' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 24.

In certain embodiments, the rAAV genome comprises a nucleotide sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 43. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 43.

In certain embodiments, the rAAV genome further comprises a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the 5' homology arm nucleotide sequence, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the 3' homology arm nucleotide sequence. In certain embodiments, the 5' ITR nucleotide sequence is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 14, and the 3' ITR nucleotide sequence is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 18.

In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 73 and/or 74. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 75 and/or 76.

In certain embodiments, the rAAV genome comprises a nucleotide sequence that is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 45. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 45. In certain embodiments, the nucleotide sequence of the rAAV genome consists of the nucleotide sequence set forth in SEQ ID NO: 45.

In certain embodiments, the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments:

(a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M;

(c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R;

(d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or

(e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C.

In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments,

(a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M;

(c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R;

(d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or

(e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C.

In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 138-736 of SEQ ID NO: 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T; the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 68 of SEQ ID NO: 16 is V; the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L; the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments:

(a) the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T, and the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q;

(b) the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I, and the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is Y;

(c) the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K;

(d) the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L, and the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S;

(e) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(f) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M;

(g) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R;

(h) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or

(i) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C.

In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the integration efficiency of the editing element into the target locus is at least 1% when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions. In certain embodiments, the allelic frequency of integration of the editing element into the target locus is at least 0.5% when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions.

In another aspect, the instant disclosure provides a pharmaceutical composition comprising an rAAV disclosed herein.

In another aspect, the instant disclosure provides a polynucleotide comprising the nucleic acid sequence set forth in SEQ ID NO: 43, 45, 51, or 52.

In another aspect, the instant disclosure provides a method for treating a subject having phenylketonuria (PKU), the method comprising administering to the subject an effective amount of an rAAV, or pharmaceutical composition disclosed herein. In certain embodiments, the rAAV or pharmaceutical composition is administered intravenously. In certain embodiments, the PKU is associated with a PAH gene mutation. In certain embodiments, the subject is a human subject.

In another aspect, the instant disclosure provides a packaging system for preparation of an rAAV, wherein the packaging system comprises: (a) a first nucleotide sequence encoding one or more AAV Rep proteins; (b) a second nucleotide sequence encoding a capsid protein disclosed herein; and (c) a third nucleotide sequence comprising an rAAV genome sequence of an rAAV disclosed herein. In certain embodiments, the packaging system comprises a first vector comprising the first nucleotide sequence and the second nucleotide sequence, and a second vector comprising the third nucleotide sequence. In certain embodiments, the packaging system further comprises a fourth nucleotide sequence comprising one or more helper virus genes. In certain embodiments, the fourth nucleotide sequence is comprised within a third vector. In certain embodiments, the fourth nucleotide sequence comprises one or more genes from a virus selected from the group consisting of adenovirus, herpes virus, vaccinia virus, and cytomegalovirus (CMV). In certain embodiments, the first vector, second vector, and/or the third vector is a plasmid.

In another aspect, the instant disclosure provides a method for recombinant preparation of an rAAV, the method comprising introducing a packaging system disclosed herein into a cell under conditions whereby the rAAV is produced.

An rAAV, pharmaceutical composition, or polynucleotide disclosed herein, for use as a medicament. An rAAV, pharmaceutical composition, or polynucleotide disclosed herein, for use in the treatment of PKU. An rAAV, pharmaceutical composition, or polynucleotide disclosed herein, for use in a method of treating a subject having PKU, the method comprising administering to the subject an effective amount of the rAAV, the pharmaceutical composition, or the polynucleotide.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic showing the gene transfer and gene editing mechanism of an rAAV as disclosed herein.

FIGS. **2**A-**2**D are schematics showing the plasmid maps of PAH-006m (FIG. **2**A), PAH-006m-LP-1 (FIG. **2**B), PAH-032h (FIG. **2**C), and hPAH-hI1C-032-LP1-SD3 (FIG. **2**D).

FIG. **3** is a plot showing the effect of PAH-006m on blood Phe levels in PAH^{enu2} mice.

FIG. **4** is a plot showing on-target insertion at the mouse PAH locus following administration of PAH-006m.

FIG. **5** is a plot showing the effect of PAH-006m on mRNA expression relative to mouse GAPDH.

FIG. **6** is a plot showing on-target insertion in FRG® mice following administration of PAH-032h as measured by species specific ddPCR editing assays.

FIG. **7** is a plot showing editing of human hepatocytes in FRG mice as measured by quantitative next generation sequencing assays.

FIGS. **8**A-**8**C are plots showing the effect of PAH-006m-LP-1 on blood Phe concentration in PAH^{enu2} mice over time. FIG. **8**A shows the full data set, while FIG. **8**B shows the data over a certain range in time with a reduced y-axis scale in order to show differences between the dose levels. FIG. **8**C shows the on-target integration of PAH-006m-LP-1 in PAH^{enu2} mice, as measured by next generation sequencing.

FIGS. **9**A-**9**L are plots showing the efficacy of the gene transfer/gene editing vector PAH-006m-LP-1 and an episomal transgene expression vector. FIGS. **9**A and **9**B are plots showing the effect of the episomal transgene expression vector and PAH-006m-LP-1, respectively, packaged in AAVHSC15 capsid, on the serum Phe levels of PAH^{enu2} mice, up to 12 weeks post-dosing at the indicated doses. FIGS. **9**C and **9**D are plots showing the effect of the episomal transgene expression vector and PAH-006m-LP-1, respectively, packaged in AAVHSC15 capsid, on the serum Tyr levels of PAH^{enu2} mice, up to 12 weeks post-dosing at the indicated doses. FIGS. **9**E and **9**F are plots showing the effect of the episomal transgene expression vector and PAH-006m-LP-1, respectively, packaged in AAVHSC15 capsid, on the level of vector genomes detected per ug of genomic DNA in PAH^{enu2} mice, at the indicated doses. FIGS. **9**G and **9**H are plots showing the effect of the episomal transgene expression vector and PAH-006m-LP-1, respectively, packaged in AAVHSC15 capsid, on the level of mRNA expression per 10 ng of total RNA detected in PAH^{enu2} mice, at the indicated doses. FIG. **9**I is a plot showing the level of on-target integration presented by the number of viral genomes per allele detected by ddPCR across various doses as indicated, at 12 weeks post-dosing of vector packaged in AAVHSC15 as indicated. FIG. **9**J is a plot showing the frequency of on-target insertion detected across various doses as indicated, at 12 weeks post-dosing of vector packaged in AAVHSC15 as indicated. FIGS. **9**K and **9**L are plots showing time courses out to 42 weeks (FIG. **9**K) or 40 weeks (FIG. **9**L) post-dosing of PAH^{enu2} mice with vector and dosage as indicated, of the results of the effect of a partial hepatectomy (PHx) on serum Phe levels. PHx or sham surgery was performed at around 2 weeks post-dosing.

FIGS. **10**A-**10**P are plots showing dose range differences between the mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1; "mouse design"), and the human-specific gene transfer/gene editing AAV vector (hPAH-hI1C-032-LP1-SD3; "human design") in 4-week (FIGS. **10**A-**10**H) or 10-week-old (FIGS. **10**I-**10**P) PAH^{enu2} mice administered the vector packaged in AAVHSC15 capsid as indicated, at the dosage as indicated.

FIGS. **11**A-**11**K are plots showing the effect the age of PAHenu2 mice has on the response to a single dose of the mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1; "mouse design"), or the human-specific gene transfer/gene editing AAV vector (hPAH-hI1C-032-LP1-SD3; "human design"). Serum Phe and Tyr levels (FIGS. **11**A-**11**D) and vector genome and mRNA levels (FIGS. **11**E-**11**K) were examined overtime for the various dosing groups set forth in Table 2.

FIGS. **12**A-**12**C are plots showing the kinetics and durability of integration over time, of PAH^{enu2} mice administered a mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1) packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg. FIGS. **12**A and **12**B are plots showing the effect of PAH-006m-LP-1 packaged in AAVHSC15 capsid on the level of vector genomes detected per ug of genomic DNA, and the level of mRNA expression detected per 10 ng of total RNA in PAH^{enu2} mice, respectively, over time. FIG. **12**C is a plot showing the frequency of on-target insertion detected at various time points post-dosing of PAH-006m-LP-1 packaged in AAVHSC15 capsid. FIGS. **12**D and **12**E are graphs showing the effect on serum Phe (FIG. **12**D) and Tyr (FIG. **12**E) in PAH^{enu2} mice administered PAH-006m-LP-1 packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg, up to 42 weeks post-injection.

FIGS. **13**A and **13**B are plots showing the effect of hPAH-hI1C-032-LP1-SD3 packaged in AAVHSC15 on the level of vector genomes detected per ug of genomic DNA, and the level of mRNA expression detected per 10 ng of total RNA in human hepatocytes isolated from HuLiv mice, respectively, at the indicated doses and timepoints. FIG. **13**C is a plot showing the frequency of on-target insertion detected in human hepatocytes isolated from HuLiv mice at various time points post-dosing of hPAH-hI1C-032-LP1-SD3 packaged in AAVHSC15, at the indicated doses.

FIGS. **14**A-**14**D are plots showing the amount of integration at predicted off-target integration sites detected in genomic DNA isolated from HuLiv mice administered the human-specific gene transfer/gene editing vector, hPAH-hI1C-032-LP1-SD3, packaged in AAVHSC15 capsid.

DETAILED DESCRIPTION

Provided herein are recombinant adeno-associated virus (rAAV) compositions that can restore PAH gene function in cells, and methods for using the same to treat diseases associated with reduction of PAH gene function (e.g., PKU). Also provided are nucleic acids, vectors, packaging systems, and methods for making the adeno-associated virus compositions.

I. DEFINITIONS

As used herein, the terms "recombinant adeno-associated virus" or "rAAV" refers to an AAV comprising a genome lacking functional rep and cap genes.

As used herein, the term "PAH gene" refers to the phenylalanine hydroxylase (PAH) gene, including but not limited to the coding regions, exons, introns, 5' UTR, 3' UTR, and transcriptional regulatory regions of the PAH gene. The human PAH gene is identified by Entrez Gene ID 5053. An exemplary nucleotide sequence of a PAH mRNA is provided as SEQ ID NO: 53. An exemplary amino acid sequence of a PAH polypeptide is provided as SEQ ID NO: 33. In certain embodiments, the PAH gene is a variant PAH gene. Variant PAH genes are known to those of skill in the art and may comprise one or more nucleotide differences as compared to the reference human genome. In certain embodiments, a variant PAH gene is a common variant observed in the general populace. For example, variant rs1522296 comprises a single nucleotide difference from the reference human genome at the genomic location in the human genome build Hg38 at chr12: 103310787. This variant is seen in >30% of the global population and has no known association to either changes in PAH expression or disease risk.

As used herein, the term "rAAV genome" refers to a recombinant AAV genome that is capable of integrating an editing element (e.g., one or more nucleotides or an internucleotide bond) via homologous recombination into a target locus to correct a genetic defect in a PAH gene. In certain embodiments, the target locus is in the human PAH gene. The skilled artisan will appreciate that the portion of an rAAV genome comprising the 5' homology arm, editing element, and 3' homology arm can be in the sense or antisense orientation relative to the target locus (e.g., the human PAH gene).

As used herein, the term "editing element" refers to the portion of an rAAV genome that when integrated at a target locus modifies the target locus. An editing element can mediate insertion, deletion, or substitution of one or more nucleotides at the target locus.

As used herein, the term "target locus" refers to a region of a chromosome or an internucleotide bond (e.g., a region or an internucleotide bond of the human PAH gene) that is modified by an editing element.

As used herein, the term "homology arm" refers to a portion of an rAAV genome positioned 5' or 3' of an editing element that is substantially identical to the genome flanking a target locus. In certain embodiments, the target locus is in a human PAH gene, and the homology arm comprises a sequence substantially identical to the genome flanking the target locus.

As used herein, the term "AAV capsid protein" refers to an AAV VP1, VP2, or VP3 capsid protein. As used herein, the term "Clade F capsid protein" refers to an AAV VP1, VP2, or VP3 capsid protein that comprises an amino acid sequence having at least 90% identity with the VP1, VP2, or VP3 amino acid sequences set forth, respectively, in amino acids 1-736, 138-736, and 203-736 of SEQ ID NO: 1 herein.

As used herein, the "percentage identity" between two nucleotide sequences or between two amino acid sequences is calculated by multiplying the number of matches between the pair of aligned sequences by 100, and dividing by the length of the aligned region, including internal gaps. Identity scoring only counts perfect matches and does not consider the degree of similarity of amino acids to one another. Note that only internal gaps are included in the length, not gaps at the sequence ends.

As used herein, the term "a disease or disorder associated with a PAH gene mutation" refers to any disease or disorder caused by, exacerbated by, or genetically linked with variation of a PAH gene. In certain embodiments, the disease or disorder associated with a PAH gene mutation is phenylketonuria (PKU).

As used herein, the term "silently altered" refers to alteration of a coding sequence or a stuffer-inserted coding sequence of a gene (e.g., by nucleotide substitution) without changing the amino acid sequence of the polypeptide encoded by the coding sequence or stuffer-inserted coding sequence. Codon alteration can be conducted by any method known in the art (e.g., as described in Mauro & Chappell (2014) Trends Mol Med. 20(11):604-13, which is incorporated by reference herein in its entirety). Such silent alteration is advantageous in that it reduces the likelihood of integration of the rAAV genome into loci of other genes or pseudogenes paralogous to the target gene. Such silent alteration also reduces the homology between the editing element and the target gene, thereby reducing undesired integration mediated by the editing element rather than by a homology arm.

As used herein, the term "coding sequence" refers to the portion of a complementary DNA (cDNA) that encodes a polypeptide, starting at the start codon and ending at the stop codon. A gene may have one or more coding sequences due to alternative splicing and/or alternative translation initiation. A coding sequence may either be wild-type or silently altered. An exemplary wild-type PAH coding sequence is set forth in SEQ ID NO: 53.

As used herein, the term "polyadenylation sequence" refers to a DNA sequence that when transcribed into RNA constitutes a polyadenylation signal sequence. The polyadenylation sequence can be native (e.g., from the PAH gene) or exogenous. The exogenous polyadenylation sequence can be a mammalian or a viral polyadenylation sequence (e.g., an SV40 polyadenylation sequence).

As used herein, the term "intron element" refers to a cis-acting nucleotide sequence, for example, a DNA sequence, that regulates (e.g., controls, increases, or reduces) expression of a transgene. In certain embodiments, an intron element is a modified intron, e.g., a synthetic intron sequence. In certain embodiments, an intron element is an exogenous intron element and is derived from an intron exogenous to the transgene it may regulate. In certain embodiments, an intron element comprises a modified splice acceptor and/or splice donor resulting in more robust splicing activity. While not wishing to be bound by theory, it is hypothesized that introns can increase transgene expression, for example, by reducing transcriptional silencing and enhancing mRNA export from the nucleus to the cytoplasm. A skilled worker will appreciate that synthetic intron sequences can be designed to mediate RNA splicing by introducing any consensus splicing motifs known in the art (e.g., in Sibley et al. (2016) *Nature Reviews Genetics,* 17, 407-21, which is incorporated by reference herein in its entirety). Exemplary intron sequences are provided in Lu et al. (2013) *Molecular Therapy* 21(5): 954-63, and Lu et al. (2017) *Hum. Gene Ther.* 28(1): 125-34, which are incorporated by reference herein in their entirety.

As used herein, the term "transcriptional regulatory element" or "TRE" refers to a cis-acting nucleotide sequence, for example, a DNA sequence, that regulates (e.g., controls, increases, or reduces) transcription of an operably linked nucleotide sequence by an RNA polymerase to form an RNA molecule. A TRE relies on one or more trans-acting molecules, such as transcription factors, to regulate transcription. Thus, one TRE may regulate transcription in different ways when it is in contact with different trans-acting molecules, for example, when it is in different types of cells. A TRE may comprise one or more promoter elements and/or enhancer elements. A skilled artisan would appreciate that the promoter and enhancer elements in a gene may be close in location, and the term "promoter" may refer to a sequence comprising a promoter element and an enhancer element. Thus, the term "promoter" does not exclude an enhancer element in the sequence. The promoter and enhancer elements do not need to be derived from the same gene or species, and the sequence of each promoter or enhancer element may be either identical or substantially identical to the corresponding endogenous sequence in the genome.

As used herein, the term "operably linked" is used to describe the connection between a TRE and a coding sequence to be transcribed. Typically, gene expression is placed under the control of a TRE comprising one or more promoter and/or enhancer elements. The coding sequence is "operably linked" to the TRE if the transcription of the coding sequence is controlled or influenced by the TRE. The promoter and enhancer elements of the TRE may be in any orientation and/or distance from the coding sequence, as long as the desired transcriptional activity is obtained. In certain embodiments, the TRE is upstream from the coding sequence.

In the instant disclosure, nucleotide positions in a PAH gene are specified relative to the first nucleotide of the start codon. The first nucleotide of a start codon is position 1; the nucleotides 5' to the first nucleotide of the start codon have negative numbers; the nucleotides 3' to the first nucleotide of the start codon have positive numbers. As used herein, nucleotide 1 of the human PAH gene is nucleotide 5,473 of the NCBI Reference Sequence: NG_008690.1, and nucleotide −1 of the human PAH gene is nucleotide 5,472 of the NCBI Reference Sequence: NG_008690.1.

In the instant disclosure, exons and introns in a PAH gene are specified relative to the exon encompassing the first nucleotide of the start codon, which is nucleotide 5473 of the NCBI Reference Sequence: NG_008690.1. The exon encompassing the first nucleotide of the start codon is exon 1. Exons 3' to exon 1 are from 5' to 3': exon 2, exon 3, etc. Introns 3' to exon 1 are from 5' to 3': intron 1, intron 2, etc. Accordingly, the PAH gene comprises from 5' to 3': exon 1, intron 1, exon 2, intron 2, exon 3, etc. As used herein, exon 1 of the human PAH gene is nucleotides 5001-5532 of the NCBI Reference Sequence: NG_008690.1, and intron 1 of the human PAH gene is nucleotides 5533-9704 of the NCBI Reference Sequence: NG_008690.1.

As used herein, the term "integration" refers to introduction of an editing element into a target locus (e.g., of a PAH gene) by homologous recombination between an rAAV genome and the target locus. Integration of an editing element can result in substitution, insertion and/or deletion of one or more nucleotides in a target locus (e.g., of a PAH gene).

As used herein, the term "integration efficiency of the editing element into the target locus" refers to the percentage of cells in a transduced population in which integration of the editing element into the target locus has occurred.

As used herein, the term "allelic frequency of integration of the editing element into the target locus" refers to the percentage of alleles in a population of transduced cells in which integration of the editing element into the target locus has occurred.

As used herein, the term "standard AAV administration conditions" refers to transduction of human hepatocytes implanted into a mouse following hepatocyte ablation, wherein the AAV is administered intravenously at a dose of 1×10^{13} vector genomes per kilogram of body weight.

As used herein, the term "effective amount" in the context of the administration of an AAV to a subject refers to the amount of the AAV that achieves a desired prophylactic or therapeutic effect.

As used herein, the term "about" or "approximately" when referring to a measurable value, such as the expression level of an IDS protein, encompasses variations of ±20% or ±10%, ±5%, ±1%, or ±0.1% of a given value or range, as are appropriate to perform the methods disclosed herein.

II. ADENO-ASSOCIATED VIRUS COMPOSITIONS

In one aspect, provided herein are novel rAAV compositions useful for restoring PAH expression in cells with reduced or otherwise defective PAH gene function. Such rAAV compositions are highly efficient at editing the genome of cells (e.g., liver cells) in a subject to express PAH under the control of a liver-specific promoter, and do not require cleavage of the genome at the target locus by the action of an exogenous nuclease (e.g., a meganuclease, a zinc finger nuclease, a transcriptional activator-like nuclease (TALEN), or an RNA-guided nuclease such as a Cas9) to facilitate such editing. Accordingly, in certain embodiments, the rAAV compositions disclosed herein do not comprise or require an exogenous nuclease or a nucleotide sequence that encodes an exogenous nuclease.

In certain embodiments, the rAAV disclosed herein comprises: (a) an AAV capsid comprising an AAV capsid protein (e.g., an AAV Clade F capsid protein); and (b) an rAAV genome comprising: (i) an editing element for editing a target locus in a PAH gene, comprising at least a portion of a PAH coding sequence operably linked to a transcriptional regulatory element; (ii) a 5' homology arm nucleotide sequence position 5' of the editing element, having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence positioned 3' of the editing element, having homology to a second genomic region 3' to the target locus. In certain embodiments, the rAAV disclosed herein has the potential to express a PAH transgene both via episomal expression and through insertion of the editing element into the genome at the target locus in the PAH gene (see, FIG. **1**). In certain embodiments, the rAAV disclosed herein allows for the expression of PAH to be maintained throughout the period of hepatic growth, during which episomal expression may be lost. Accordingly, the rAAV compositions are particularly useful for treating juvenile PKU.

A capsid protein from any capsid known in the art can be used in the rAAV compositions disclosed herein, including, without limitation, a capsid protein from an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, or AAV9 serotype. For example, in certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, wherein: the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C. In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

For example, in certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, wherein: the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C. In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

For example, in certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the capsid protein comprises an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, wherein: the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T; the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 68 of SEQ ID NO: 16 is V; the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L; the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ

ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T, and the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I, and the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is Y. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L, and the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R. In certain embodiments, the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C. In certain embodiments, the capsid protein comprises the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the AAV capsid comprises two or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 6, 7, 10, 11, 12, 13, 15, 16, or 17; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17. In certain embodiments, the AAV capsid comprises: (a) a capsid protein having an amino acid sequence consisting of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 6, 7, 10, 11, 12, 13, 15, 16, or 17; (b) a capsid protein having an amino acid sequence consisting of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17; and (c) a capsid protein having an amino acid sequence consisting of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 203-736 of SEQ ID NO: 8; (b) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 138-736 of SEQ ID NO: 8; and (c) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 1-736 of SEQ ID NO: 8. In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 8; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 8; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 8. In certain embodiments, the AAV capsid comprises two or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 8; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 8; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 8. In certain embodiments, the AAV capsid comprises: (a) a capsid protein having an amino acid sequence consisting of amino acids 203-736 of SEQ ID NO: 8; (b) a capsid protein having an amino acid sequence consisting of amino acids 138-736 of SEQ ID NO: 8; and (c) a capsid protein having an amino acid sequence consisting of amino acids 1-736 of SEQ ID NO: 8.

In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 203-736 of SEQ ID NO: 11; (b) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 138-736 of SEQ ID NO: 11; and (c) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 1-736 of SEQ ID NO: 11. In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 11; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 11; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 11. In certain embodiments, the AAV capsid comprises two or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 11; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 11; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 11. In certain embodiments, the AAV capsid comprises: (a) a capsid protein having an amino acid sequence consisting of amino acids 203-736 of SEQ ID NO: 11; (b) a capsid protein having an amino acid sequence consisting of amino acids 138-736 of SEQ ID NO: 11; and (c) a capsid protein having an amino acid sequence consisting of amino acids 1-736 of SEQ ID NO: 11.

In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 203-736 of SEQ ID NO: 13; (b) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 138-736 of SEQ ID NO: 13; and (c) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the sequence of amino acids 1-736 of SEQ ID NO: 13. In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 13; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 13; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 13. In certain embodiments, the AAV capsid comprises two or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 13; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 13; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 13. In certain embodiments, the AAV capsid comprises: (a) a capsid protein having an amino acid sequence consisting of amino acids 203-736 of SEQ ID NO: 13; (b) a capsid protein having an amino acid sequence consisting of amino acids 138-736 of SEQ ID NO: 13; and (c) a capsid protein having an amino acid sequence consisting of amino acids 1-736 of SEQ ID NO: 13.

In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the sequence of amino acids 203-736 of SEQ ID NO: 16; (b) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the sequence of amino acids 138-736 of SEQ ID NO: 16; and (c) a capsid protein comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity with the sequence of amino acids 1-736 of SEQ ID NO: 16. In certain embodiments, the AAV capsid comprises one or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 16; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 16; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 16. In certain embodiments, the AAV capsid comprises two or more of: (a) a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 16; (b) a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 16; and (c) a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 16. In certain embodiments, the AAV capsid comprises: (a) a capsid protein having an amino acid sequence consisting of amino acids 203-736 of SEQ ID NO: 16; (b) a capsid protein having an amino acid sequence consisting of amino acids 138-736 of SEQ ID NO: 16; and (c) a capsid protein having an amino acid sequence consisting of amino acids 1-736 of SEQ ID NO: 16.

rAAV genomes useful in the AAV compositions disclosed herein generally comprise: (i) an editing element for editing a target locus in a PAH gene, comprising at least a portion of a PAH coding sequence operably linked to a transcriptional regulatory element; (ii) a 5' homology arm nucleotide sequence position 5' of the editing element, having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence positioned 3' of the editing element, having homology to a second genomic region 3' to the target locus. In certain embodiments, the rAAV genome comprises a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the 5' homology arm nucleotide sequence, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the 3' homology arm nucleotide sequence.

Editing elements used in the rAAV genomes disclosed herein can mediate insertion, deletion, or substitution of one or more nucleotides at the target locus.

In certain embodiments, when correctly integrated by homologous recombination at the target locus, the editing element inserts a nucleotide sequence comprising at least a portion of a PAH coding sequence into a PAH gene. In certain embodiments, the editing element comprises a PAH coding sequence (e.g., a complete PAH coding sequence).

In certain embodiments, the PAH coding sequence encodes a wild-type PAH polypeptide (e.g., having the amino acid sequence set forth in SEQ ID NO: 33). In certain embodiments, the PAH coding sequence is wild-type (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 53). In certain embodiments, the PAH coding sequence is silently altered to be less than 100% (e.g., less than 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50%) identical to the corresponding exons of the wild-type PAH gene. In certain embodiments, the PAH coding sequence comprises or consists of a nucleotide sequence that is at least 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the nucleotide sequence set forth in SEQ ID NO: 28, 63, or 83. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28. In certain embodiments, the PAH coding sequence consists of the nucleotide sequence set forth in SEQ ID NO: 28. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 63. In certain embodiments, the PAH coding sequence consists of the nucleotide sequence set forth in SEQ ID NO: 63. In certain embodiments, the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 83. In certain embodiments, the PAH coding sequence consists of the nucleotide sequence set forth in SEQ ID NO: 83.

In certain embodiments, rAAV genomes useful in the AAV compositions disclosed herein comprise a transcriptional regulatory element (TRE) operably linked to at least a portion of a PAH coding sequence. In certain embodiments, rAAV genomes useful in the AAV compositions disclosed herein comprise from 5' to 3': a TRE, and the at least a portion of a PAH coding sequence.

The rAAV genome can be used to express PAH in any mammalian cells (e.g., human cells). Thus, the TRE can be active in any mammalian cells (e.g., human cells). In certain embodiments, the TRE is active in a broad range of human cells. Such TREs may comprise constitutive promoter and/or enhancer elements including cytomegalovirus (CMV) promoter/enhancer (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 54, 55, or 56), SV40 promoter, chicken ACTB promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 47 or 57), JeT promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 58), smCBA promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 59), human elongation factor 1 alpha (EF1α) promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 39), minute virus of mouse (MVM) intron which comprises transcription factor binding sites (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 61), human phosphoglycerate kinase (PGK1) promoter, human ubiquitin C (Ubc) promoter, human beta actin promoter, human neuron-specific enolase (ENO2) promoter, human beta-glucuronidase (GUSB) promoter, a rabbit beta-globin element (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41 or 62), human calmodulin 1 (CALM1) promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 44), and/or human Methyl-CpG Binding Protein 2 (MeCP2) promoter. Any of these TREs can be combined in any order to drive efficient transcription. For example, an rAAV genome may comprise a CMV enhancer, a CBA promoter, and the splice acceptor from exon 3 of the rabbit beta-globin gene, collectively called a CAG promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 42 or 64). For example, an rAAV genome may comprise a hybrid of CMV enhancer and CBA promoter followed by a splice donor and splice acceptor, collectively called a CASI promoter region (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 48 or 65).

Alternatively, the TRE may be a tissue-specific TRE, i.e., it is active in specific tissue(s) and/or organ(s). A tissue-specific TRE comprises one or more tissue-specific promoter and/or enhancer elements, and optionally one or more constitutive promoter and/or enhancer elements. A skilled artisan would appreciate that tissue-specific promoter and/or enhancer elements can be isolated from genes specifically expressed in the tissue by methods well known in the art.

In certain embodiments, the TRE is liver-specific (e.g., hepatocyte-specific). Exemplary liver-specific TREs may comprise one or more elements selected from the group consisting of human albumin promoter, human transthyretin (TTR) promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 66), human APOE/C-I hepatic control region (HCR) 1 or 2 (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 or 68), human APOH promoter, and human SERPINA1 (hAAT) promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 26, 69 or 70) or a hepatic specific regulatory module thereof (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 71). In certain embodiments, an hAAT promoter region comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 72. More liver-specific promoter elements are disclosed in WO 2009/130208 and Kramer et al. *Molecular Therapy* (2003) 7, 375-385, which are incorporated by reference herein in their entirety.

In certain embodiments, the TRE is kidney-specific (e.g., renal epithelial cell-specific). Exemplary kidney-specific TREs may comprise one or more elements selected from the group consisting of human nephrin promoter, human parathyroid hormone receptor promoter, human uromodulin promoter, and human SLC12A1 promoter. In certain embodiments, the TRE is brain-specific (e.g., neuron-specific, glial cell-specific, astrocyte-specific, oligodendrocyte-specific, microglia-specific and/or central nervous system-specific). Exemplary brain-specific TREs may comprise one or more elements selected from the group consisting of human glial fibrillary acidic protein (GFAP) promoter and human synapsin 1 (SYN1) promoter. More brain-specific promoter elements are disclosed in WO 2016/100575A1, which is incorporated by reference herein in its entirety.

In certain embodiments, the rAAV genome comprises two or more TREs, optionally comprising at least one of the TREs disclosed above. A skilled person in the art would appreciate that any of these TREs can be combined in any order, and combinations of a constitutive TRE and a tissue-specific TRE can drive efficient and tissue-specific transcription. For example, in certain embodiments, the rAAV genome comprises a human HCR1 (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 or 68) and a human EF-1α promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 39), optionally wherein the human HCR1 is 5' to the human EF-1α promoter. In certain embodiments, the rAAV genome comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence nucleotide set forth in SEQ ID NO: 60.

Similarly, combinations of two or more tissue-specific TREs can drive efficient and tissue-specific transcription. For example, in certain embodiments, the rAAV genome comprises a human HCR1 (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25) and a hAAT promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 26), optionally wherein the human HCR1 is 5' to the hAAT promoter. In certain embodiments, the rAAV genome comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 27. In certain embodiments, the rAAV genome comprises a human HCR1 (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 25) and a hAAT promoter (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 26), optionally wherein the human HCR1 is 5' to the hAAT promoter. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 27.

In certain embodiments, the rAAV genome comprises a hepatic specific regulatory module of hAAT promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 71) and a human TTR promoter (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 66), optionally wherein the hepatic specific regulatory module is 5' to the human TTR promoter. In certain embodiments, the rAAV genome comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the nucleotide sequence set forth in SEQ ID NO: 67. In certain embodiments, the rAAV genome comprises a hepatic specific regulatory module of hAAT promoter (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 71) and a human TTR promoter (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 66), optionally wherein the hepatic specific regulatory module is 5' to the human TTR promoter. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 67.

In certain embodiments, the rAAV genome further comprises an intron element 5' to the at least a portion of a PAH coding sequence. Such intron elements can increase transgene expression, for example, by reducing transcriptional silencing and enhancing mRNA export from the nucleus to the cytoplasm. In certain embodiments, the rAAV genome comprises from 5' to 3': a TRE, an intron element, and the at least a portion of a PAH coding sequence.

The intron element can comprise at least a portion of a native intron sequence of the PAH gene, or the intron element can be an exogenous intron element (e.g., comprising at least an intron sequence from a different species or a different gene from the same species, and/or a synthetic intron sequence). In certain embodiments, the intron element is an exogenous intron element comprising at least a portion of an intron sequence from a different species. In certain embodiments, the intron element is an exogenous intron element comprising at least a portion of an intron sequence from a different gene from the same species. In certain embodiments, the intron element is an exogenous intron element comprising a synthetic intron sequence. In certain embodiments, the intron element is an exogenous intron element comprising a combination of at least an intron sequence from a different species or a different gene from the same species, and/or a synthetic intron sequence.

A skilled worker will appreciate that intron elements can be designed to mediate RNA splicing by introducing any consensus splicing motifs known in the art (e.g., in Sibley et al. (2016) *Nature Reviews Genetics,* 17, 407-21, which is incorporated by reference herein in its entirety). Exemplary intron sequences are provided in Lu et al. (2013) *Molecular Therapy* 21(5): 954-63, and Lu et al. (2017) *Hum. Gene Ther.* 28(1): 125-34, which are incorporated by reference herein in their entirety.

In certain embodiments, the rAAV genome comprises an exogenous intron element. In certain embodiments, the rAAV comprises an SV40 intron element (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 29) or a minute virus of mouse (MVM) intron (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 61). In certain embodiments, the rAAV genome comprises an SV40 intron element (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 29) or a minute virus of mouse (MVM) intron element (e.g., comprising the nucleotide sequence set forth in SEQ ID NO: 61).

In certain embodiments, the rAAV genome disclosed herein further comprises a transcription terminator (e.g., a polyadenylation sequence). In certain embodiments, the transcription terminator is 3' to the at least a portion of a PAH coding sequence. The transcription terminator may be any sequence that effectively terminates transcription, and a skilled artisan would appreciate that such sequences can be isolated from any genes that are expressed in the cell in which transcription of the at least a portion of a PAH coding sequence is desired. In certain embodiments, the transcription terminator comprises a polyadenylation sequence. In certain embodiments, the polyadenylation sequence is identical or substantially identical to the endogenous polyadenylation sequence of the human PAH gene. In certain embodiments, the polyadenylation sequence is an exogenous polyadenylation sequence. In certain embodiments, the polyadenylation sequence is an SV40 polyadenylation sequence (e.g., comprising a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31, 34, or 35, or a nucleotide sequence complementary thereto). In certain embodiments, the polyadenylation sequence comprises the nucleotide sequence set forth in SEQ ID NO: 31. In certain embodiments, the polyadenylation sequence consists of the nucleotide sequence set forth in SEQ ID NO: 31.

In certain embodiments, the rAAV genome comprises from 5' to 3': a TRE, an intron element, at least a portion of a PAH coding sequence, and a polyadenylation sequence. In certain embodiments, the TRE has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 25-27, 30, 36, 39, 40-42, 44, 46-49, 54-60, or 62-72; the intron element has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 29 or 61; the at least a portion of a PAH coding sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 28; and/or the polyadenylation sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to any one of SEQ ID NOs: 31, 34, or 35. In certain embodiments, the TRE comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 25-27, 30, 36, 39, 40-42, 44, 46-49, 54-60, and 62-72; the intron element comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 29 and 61; the at least a portion of a PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28; and/or the polyadenylation sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 34, and 35.

In certain embodiments, the TRE comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 25, 26, or 27; the intron element comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 29; the at least a portion of a PAH coding sequence comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 28; and/or the polyadenylation sequence comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 31. In certain embodiments, the TRE comprises from 5' to 3' the nucleotide sequence set forth in SEQ ID NO: 25, and the nucleotide sequence set forth in SEQ ID NO: 26 (e.g., the TRE comprises the nucleotide sequence set forth in SEQ ID NO: 27); the intron element comprises the nucleotide sequence set forth in SEQ ID NO: 29; the at least a portion of a PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28; and/or the polyadenylation sequence comprises the nucleotide sequence set forth in SEQ ID NO: 31.

Homology arms used in the rAAV genomes disclosed herein can be directed to any region of the PAH gene or a gene nearby on the genome. The precise identity and positioning of the homology arms are determined by the identity of the editing element and/or the target locus.

Homology arms employed in the rAAV genomes disclosed herein are substantially identical to the genome flanking a target locus (e.g., a target locus in a PAH gene). In certain embodiments, the 5' homology arm has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to a first genomic region 5' to the target locus. In certain embodiments, the 5' homology arm has 100% nucleotide sequence identity to the first genomic region. In certain embodiments, the 3' homology arm has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to a second genomic region 3' to the target locus. In certain embodiments, the 3' homology arm has 100% nucleotide sequence identity to the second genomic region. In certain embodiments, the 5' and 3' homology arms are each at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) identical to the first and second genomic regions flanking the target locus (e.g., a target locus in the PAH gene), respectively. In certain embodiments, the 5' and 3' homology arms are each 100% identical to the first and second genomic regions flanking the target locus (e.g., a target locus in the PAH gene), respectively. In certain embodiments, differences in nucleotide sequences of the 5' homology arm and/or the 3' homology arm and the corresponding regions the genome flanking a target locus comprise, consist essentially of, or consist of non-coding differences in nucleotide sequences.

The skilled worker will appreciate that homology arms do not need to be 100% identical to the genomic sequence flanking the target locus to be able to mediate integration of an editing element into that target locus by homologous recombination. For example, the homology arms can comprise one or more genetic variations in the human population, and/or one or more modifications (e.g., nucleotide substitutions, insertions, or deletions) designed to improve expression level or specificity. Human genetic variations include both inherited variations and de novo variations that are private to the target genome, and encompass simple nucleotide polymorphisms, insertions, deletions, rearrangements, inversions, duplications, micro-repeats, and combinations thereof. Such variations are known in the art, and can be found, for example, in the databases of dnSNP (see Sherry et al. *Nucleic Acids Res.* 2001; 29(1):308-11), the Database of Genomic Variants (see *Nucleic Acids Res.* 2014; 42 (Database issue): D986-92), ClinVar (see *Nucleic Acids Res.* 2014; 42 (Database issue): D980-D985), Genbank (see *Nucleic Acids Res.* 2016; 44 (Database issue): D67-D72), ENCODE (genome.ucsc.edu/encode/terms.html), JASPAR (see *Nucleic Acids Res.* 2018; 46(D1): D260-D266), and PROMO (see Messeguer et al. *Bioinformatics* 2002; 18(2): 333-334; Farré et al. *Nucleic Acids Res.* 2003; 31(13):3651-3653), each of which is incorporated herein by reference. The skilled worker will further appreciate that in situations where a homology arm is not 100% identical to the genomic sequence flanking the target locus, homologous recombination between the homology arm and the genome may alter the genomic sequence flanking the target locus such that it becomes identical to the sequence of the homology arm used.

In certain embodiments, the first genomic region 5' to the target locus is located in a first editing window, wherein the first editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37. In certain embodiments, the second genomic region 3' to the target locus is located in a second editing window, wherein the second editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38. In certain embodiments, the first genomic region 5' to the target locus is located in a first editing window, wherein the first editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37; and the second genomic region 3' to the target locus is located in a second editing window, wherein the second editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38.

In certain embodiments, the first and second editing windows are different. In certain embodiments, the first editing window is located 5' to the second editing window. In certain embodiments, the first genomic region consists of a sequence shorter than the sequence of the first editing window in which the first genomic region is located. In certain embodiments, the first genomic region consists of the sequence of the first editing window in which the first genomic region is located. In certain embodiments, the second genomic region consists of a sequence shorter than the sequence of the second editing window in which the second genomic region is located. In certain embodiments, the second genomic region consists of the sequence of the second editing window in which the second genomic region is located.

In certain embodiments, the first and second editing windows are the same. In certain embodiments, the target locus is an internucleotide bond or a nucleotide sequence in the editing window, wherein the first genomic region consists of a first portion of the editing window 5' to the target locus, and the second genomic region consists of a second portion of the editing window 3' to the target locus. In certain embodiments, the first portion of the editing window consists of the sequence from the 5' end of the editing window to the nucleotide adjacently 5' to the target locus. In certain embodiments, the second portion of the editing window consists of the sequence from the nucleotide adjacently 3' to the target locus to the 3' end of the editing window. In certain embodiments, the first portion of the editing window consists of the sequence from the 5' end of the editing window to the nucleotide adjacently 5' to the target locus, and the second portion of the editing window consists of the sequence from the nucleotide adjacently 3' to the target locus to the 3' end of the editing window. In certain embodiments, the editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37 or 38. In certain embodiments, the first and second portions of the editing windows have substantially equal lengths (e.g., the ratio of the length of the shorter portion to the length of the longer portion is greater than 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, 0.96, 0.97, 0.98, or 0.99).

In certain embodiments, the 5' homology arm has a length of about 50 to about 4000 nucleotides (e.g., about 100 to about 3000, about 200 to about 2000, about 500 to about 1000 nucleotides). In certain embodiments, the 5' homology arm has a length of about 800 nucleotides. In certain embodiments, the 5' homology arm has a length of about 100 nucleotides. In certain embodiments, the 3' homology arm has a length of about 50 to about 4000 nucleotides (e.g., about 100 to about 3000, about 200 to about 2000, about 500 to about 1000 nucleotides). In certain embodiments, the 3' homology arm has a length of about 800 nucleotides. In certain embodiments, the 3' homology arm has a length of about 100 nucleotides. In certain embodiments, each of the 5' and 3' homology arms independently has a length of about 50 to about 4000 nucleotides (e.g., about 100 to about 3000, about 200 to about 2000, about 500 to about 1000 nucleotides). In certain embodiments, each of the 5' and 3' homology arms independently has a length of about 800 nucleotides.

In certain embodiments, the 5' and 3' homology arms have substantially equal nucleotide lengths. In certain embodiments, the 5' and 3' homology arms have asymmetrical nucleotide lengths. In certain embodiments, the asymmetry in nucleotide length is defined by a difference between the 5' and 3' homology arms of up to 90% in the length, such as up to an 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% difference in the length.

In certain embodiments, the 5' homology arm has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to the nucleotide sequence set forth in SEQ ID NO: 37. In certain embodiments, the 5' homology arm further comprises one or more genetic variations in the human population. In certain embodiments, the 5' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 23. In certain embodiments, the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 23.

In certain embodiments, the 3' homology arm has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to the nucleotide sequence set forth in SEQ ID NO: 38. In certain embodiments, the 3' homology arm further comprises one or more genetic variations in the human population. In certain embodiments, the 3' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 24. In certain embodiments, the 3' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 24.

In certain embodiments, the 5' homology arm and the 3' homology arm each has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to the nucleotide sequences set forth in SEQ ID NOs: 37 and 38, respectively. In certain embodiments, the 5' homology arm and the 3' homology arm each has at least about 90% (e.g., at least about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) nucleotide sequence identity to the nucleotide sequences set forth in SEQ ID NOs: 23 and 24, respectively. In certain embodiments, the 5' homology arm and the 3' homology arm comprise the nucleotide sequences set forth in SEQ ID NOs: 37 and 38, 23 and 24, 37 and 24, or 23 and 38, respectively. In certain embodiments, the 5' homology arm and the 3' homology arm consist of the nucleotide sequences set forth in SEQ ID NOs: 37 and 38, 23 and 24, 37 and 24, or 23 and 38, respectively.

In certain embodiments, the rAAV genome comprises a nucleotide sequence at least 80% (e.g., at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%. 88%, 89%, 90%. 91% 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%) identical to SEQ ID NO: 43. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 43. In certain embodiments, the rAAV genome consists of the nucleotide sequence set forth in SEQ ID NO: 43.

In certain embodiments, the rAAV genomes disclosed herein further comprise a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the TRE, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the PAH coding sequence. ITR sequences from any AAV serotype or variant thereof can be used in the rAAV genomes disclosed herein. The 5' and 3' ITR can be from an AAV of the same serotype or from AAVs of different serotypes. Exemplary ITRs for use in the rAAV genomes disclosed herein are set forth in SEQ ID NOs: 14, 18, 19, 20, 21, and 32, herein.

In certain embodiments, the 5' ITR or 3' ITR is from AAV2. In certain embodiments, both the 5' ITR and the 3' ITR are from AAV2. In certain embodiments, the 5' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 14, or the 3' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 18. In certain embodiments, the 5' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 14, and the 3' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 18. In certain embodiments, the rAAV genome comprises a nucleotide sequence set forth in SEQ ID NO: 43, a 5' ITR nucleotide sequence having the sequence of SEQ ID NO: 14, and a 3' ITR nucleotide sequence having the sequence of SEQ ID NO: 18.

In certain embodiments, the 5' ITR or 3' ITR are from AAV5. In certain embodiments, both the 5' ITR and 3' ITR are from AAV5. In certain embodiments, the 5' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 20, or the 3' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 21. In certain embodiments, the 5' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 20, and the 3' ITR nucleotide sequence has at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 21. In certain embodiments, the rAAV genome comprises a nucleotide sequence set forth in any one of SEQ ID NO: 43, a 5' ITR nucleotide sequence having the sequence of SEQ ID NO: 20, and a 3' ITR nucleotide sequence having the sequence of SEQ ID NO: 21.

In certain embodiments, the 5' ITR nucleotide sequence and the 3' ITR nucleotide sequence are substantially complementary to each other (e.g., are complementary to each other except for mismatch at 1, 2, 3, 4, or 5 nucleotide positions in the 5' or 3' ITR).

In certain embodiments, the 5' ITR or the 3' ITR is modified to reduce or abolish resolution by Rep protein ("non-resolvable ITR"). In certain embodiments, the non-resolvable ITR comprises an insertion, deletion, or substitution in the nucleotide sequence of the terminal resolution site. Such modification allows formation of a self-complementary, double-stranded DNA genome of the AAV after the rAAV genome is replicated in an infected cell. Exemplary non-resolvable ITR sequences are known in the art (see e.g., those provided in U.S. Pat. Nos. 7,790,154 and 9,783,824, which are incorporated by reference herein in their entirety). In certain embodiments, the 5' ITR comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 19. In certain embodiments, the 5' ITR consists of a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 19. In certain embodiments, the 5' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 19. In certain embodiments, the 3' ITR comprises a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32. In certain embodiments, the 5' ITR consists of a nucleotide sequence at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32. In certain embodiments, the 3' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 32. In certain embodiments, the 5' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 19, and the 3' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 32. In certain embodiments, the 5' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 19, and the 3' ITR consists of the nucleotide sequence set forth in SEQ ID NO: 32.

In certain embodiments, the 5' ITR is flanked by an additional nucleotide sequence derived from a wild-type AAV2 genomic sequence. In certain embodiments, the 5' ITR is flanked by an additional 46 bp sequence derived from a wild-type AAV2 sequence that is adjacent to a wild-type AAV2 ITR in an AAV2 genome. In certain embodiments, the additional 46 bp sequence is 3' to the 5' ITR in the rAAV genome. In certain embodiments, the 46 bp sequence consists of the nucleotide sequence set forth in SEQ ID NO: 74.

In certain embodiments, the 3' ITR is flanked by an additional nucleotide sequence derived from a wild-type AAV2 genomic sequence. In certain embodiments, the 3' ITR is flanked by an additional 37 bp sequence derived from a wild-type AAV2 sequence that is adjacent to a wild-type AAV2 ITR in an AAV2 genome. See, e.g., Savy et al. *Human Gene Therapy Methods* (2017) 28(5): 277-289 (which is hereby incorporated by reference herein in its entirety). In certain embodiments, the additional 37 bp sequence is 5' to the 3' ITR in the rAAV genome. In certain embodiments, the 37 bp sequence consists of the nucleotide sequence set forth in SEQ ID NO: 73.

In certain embodiments, the 5' homology arm has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleotide sequence identity to the nucleotide sequence set forth in SEQ ID NO: 37. In certain embodiments, the 5' homology arm further comprises one or more genetic variations in the human population. In certain embodiments, the 5' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 23. In certain embodiments, the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 23.

In certain embodiments, the 3' homology arm has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleotide sequence identity to the nucleotide sequence set forth in SEQ ID NO: 38. In certain embodiments, the 3' homology arm further comprises one or more genetic variations in the human population. In certain embodiments, the 3' homology arm comprises the nucleotide sequence set forth in SEQ ID NO: 24. In certain embodiments, the 3' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 24.

In certain embodiments, the rAAV genome comprises from 5' to 3': a 5' homology arm, a 5' ITR, a TRE, an intron element, at least a portion of a PAH coding sequence, a polyadenylation sequence, a 3' ITR, and/or a 3' homology arm. In certain embodiments, the 5' homology arm has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 37 or 23; the 5' ITR has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 14, 19, or 20; the TRE has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 25, 26, 27, 30, 36, 39, 40, 41, 42, 44, 46, 47, 48, 49, 54, 55, 56, 57, 58, 59, 60, 62, 64, 65, 66, 67, 68, 69, 70, 72, or 72; the intron element has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 29 or 61; the at least a portion of a PAH coding sequence has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 28;

the polyadenylation sequence has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 31, 34, or 35; the 3' ITR has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 18, 21, or 32; and/or the 3' homology arm has at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 38 or 24.

In certain embodiments, the 5' homology arm comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 37 and 23; the 5' ITR comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 14, 19, or 20; the TRE comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 25-27, 30, 36, 39, 40-42, 44, 46-49, 54-60, and 62-72; the intron comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 29 and 61; the at least a portion of a PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28; the polyadenylation sequence comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 31, 34, and 35; the 3 ITR comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 18, 21, and 32; and/or the 3' homology arm comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 38 and 24.

In certain embodiments, the 5' homology arm comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 23; the 5' ITR comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 14; the TRE comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 25, 26, or 27; the intron element comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 29; the at least a portion of a PAH coding sequence comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 28; the polyadenylation sequence comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 31; the 3' ITR comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 18; and/or the 5' homology arm comprises or consists of the nucleotide sequence set forth in SEQ ID NO: 24.

In certain embodiments, the rAAV genome comprises from 5' to 3': the 5' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 23; the 5' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 14; the TRE comprising from 5' to 3' the nucleotide sequence set forth in SEQ ID NO: 25, and the nucleotide sequence set forth in SEQ ID NO: 26 (e.g., the TRE comprises the nucleotide sequence set forth in SEQ ID NO: 27); the intron element comprising the nucleotide sequence set forth in SEQ ID NO: 29; the at least a portion of a PAH coding sequence comprising the nucleotide sequence set forth in SEQ ID NO: 28; the polyadenylation sequence comprising the nucleotide sequence set forth in SEQ ID NO: 31; the 3' ITR comprising of the nucleotide sequence set forth in SEQ ID NO: 18; and the 5' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 24.

In certain embodiments, the rAAV genome comprises a nucleotide sequence at least 80% (e.g., at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%. 88%, 89%, 90%. 91% 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to SEQ ID NO: 45. In certain embodiments, the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 45. In certain embodiments, the rAAV genome consists of the nucleotide sequence set forth in SEQ ID NO: 45.

In another aspect, provided herein is a polynucleotide comprising a nucleic acid sequence that is at least 80% (e.g., at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%. 88%, 89%, 90%. 91% 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the nucleic acid sequence set forth in SEQ ID NO: 28, 43, 45, 51, or 52. In certain embodiments, the polynucleotide comprises or consists of the nucleic acid sequence set forth in SEQ ID NO: 43, 45, 51, or 52.

In another aspect, the instant disclosure provides pharmaceutical compositions comprising an AAV as disclosed herein together with a pharmaceutically acceptable excipient, adjuvant, diluent, vehicle or carrier, or a combination thereof. A "pharmaceutically acceptable carrier" includes any material which, when combined with an active ingredient of a composition, allows the ingredient to retain biological activity and without causing disruptive physiological reactions, such as an unintended immune reaction. Pharmaceutically acceptable carriers include water, phosphate buffered saline, emulsions such as oil/water emulsion, and wetting agents. Compositions comprising such carriers are formulated by well-known conventional methods such as those set forth in *Remington's Pharmaceutical Sciences*, current Ed., Mack Publishing Co., Easton Pa. 18042, USA; A. Gennaro (2000) "*Remington: The Science and Practice of Pharmacy,"* 20th edition, Lippincott, Williams, & Wilkins; *Pharmaceutical Dosage Forms and Drug Delivery Systems* (1999) H. C. Ansel et al, 7th ed., Lippincott, Williams, & Wilkins; and *Handbook of Pharmaceutical Excipients* (2000) A. H. Kibbe et al, 3rd ed. Amer. *Pharmaceutical Assoc.*

In another aspect, the instant disclosure provides a polynucleotide comprising a coding sequence encoding a human PAH protein or a fragment thereof, wherein the coding sequence has been silently altered to have less than 100% (e.g., less than 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50%) identical to a wild-type human PAH gene. In certain embodiments, the polynucleotide comprises the nucleotide sequence set forth in SEQ ID NO: 28. The polynucleotide can comprise DNA, RNA, modified DNA, modified RNA, or a combination thereof. In certain embodiments, the polynucleotide is an expression vector.

The AAV compositions disclosed herein are particularly advantageous in that they are capable of editing a PAH gene in a cell with high efficiency both in vivo and in vitro. In certain embodiments, the integration efficiency of the editing element into the target locus is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions. In certain embodiments, the allelic frequency of integration of the editing element into the target locus is at least 0.5% (e.g., at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions.

Any methods of determining the efficiency of editing of the PAH gene can be employed. In certain embodiments, individual cells are separated from the population of transduced cells and subject to single-cell PCR using PCR primers that can identify the presence of an editing element correctly integrated into the target locus of the PAH gene. Such method can further comprise single-cell PCR of the same cells using PCR primers that selectively amplify an unmodified target locus. In this way, the genotype of the cells can be determined. For example, if the single cell PCR showed that a cell has both an edited target locus and an unmodified target locus, then the cell would be considered heterozygous for the edited PAH gene.

Additionally or alternatively, in certain embodiments, linear amplification mediated PCR (LAM-PCR), quantitative PCR (qPCR) or digital droplet PCR (ddPCR) can be performed on DNA extracted from the population of transduced cells using primers and probes that only detect edited PAH alleles. Such methods can further comprise an additional qPCR or ddPCR (either in the same reaction or a separate reaction) to determine the number of total genomes in the sample and the number of unedited PAH alleles. These numbers can be used to determine the allelic frequency of integration of the editing element into the target locus.

Additionally or alternatively, in certain embodiments, the PAH locus can be amplified from DNA extracted from the population of transduced cells either by PCR using primers that bind to regions of the PAH gene flanking the target locus, or by LAM-PCR using a primer that binds a region within the rAAV genome (e.g., a region comprising an exogenous sequence non-native to the locus). The resultant PCR amplicons can be individually sequenced using single molecule next generation sequencing (NGS) techniques to determine the relative number of edited and unedited PAH alleles present in the population of transduced cells. These numbers can be used to determine the allelic frequency of integration of the editing element into the target locus.

In another aspect, the instant disclosure provides pharmaceutical compositions comprising an AAV as disclosed herein together with a pharmaceutically acceptable excipient, adjuvant, diluent, vehicle or carrier, or a combination thereof. A "pharmaceutically acceptable carrier" includes any material which, when combined with an active ingredient of a composition, allows the ingredient to retain biological activity and without causing disruptive physiological reactions, such as an unintended immune reaction. Pharmaceutically acceptable carriers include water, phosphate buffered saline, emulsions such as oil/water emulsion, and wetting agents. Compositions comprising such carriers are formulated by well-known conventional methods such as those set forth in *Remington's Pharmaceutical Sciences*, current Ed., Mack Publishing Co., Easton Pa. 18042, USA; A. Gennaro (2000) "*Remington: The Science and Practice of Pharmacy,*" 20th edition, Lippincott, Williams, & Wilkins; *Pharmaceutical Dosage Forms and Drug Delivery Systems* (1999) H. C. Ansel et al, 7th ed., Lippincott, Williams, & Wilkins; and *Handbook of Pharmaceutical Excipients* (2000) A. H. Kibbe et al, 3rd ed. Amer. Pharmaceutical Assoc.

III. METHODS OF USE

In another aspect, the instant disclosure provides methods for restoring PAH gene function in a cell. The methods generally comprise transducing the cell with an rAAV as disclosed herein. Such methods are highly efficient at editing the PAH gene function in a cell, and do not require cleavage of the genome at the target locus by the action of an exogenous nuclease (e.g., a meganuclease, a zinc finger nuclease, a transcriptional activator-like nuclease (TALEN), or an RNA-guided nuclease such as a Cas9) to facilitate such correction. Accordingly, in certain embodiments, the methods disclosed herein involve transducing the cell with an rAAV as disclosed herein without co-transducing or co-administering an exogenous nuclease or a nucleotide sequence that encodes an exogenous nuclease.

The methods disclosed herein can be applied to any cell harboring a mutation in the PAH gene. The skilled worker will appreciate that cells that actively express PAH are of particular interest. Accordingly, in certain embodiments, the method is applied to cells in the liver, kidney, brain, pituitary gland, adrenal gland, pancreas, urinary bladder, gallbladder, colon, small intestine, or breast. In certain embodiments, the method is applied to hepatocytes and/or renal cells.

The methods disclosed herein can be performed in vitro for research purposes or can be performed ex vivo or in vivo for therapeutic purposes.

In certain embodiments, the cell to be transduced is in a mammalian subject and the AAV is administered to the subject in an amount effective to transduce the cell in the subject. Accordingly, in certain embodiments, the instant disclosure provides a method for treating a subject having a disease or disorder associated with a PAH gene mutation, the method generally comprising administering to the subject an effective amount of an rAAV as disclosed herein. The subject can be a human subject or a rodent subject (e.g., a mouse) containing human liver cells. Suitable mouse subjects include without limitation, mice into which human liver cells (e.g., human hepatocytes) have been engrafted. Any disease or disorder associated with a PAH gene mutation can be treated using the methods disclosed herein. Suitable diseases or disorders include, without limitation, phenylketonuria. In certain embodiments, the cell is transduced without co-transducing or co-administering an exogenous nuclease or a nucleotide sequence that encodes an exogenous nuclease.

The methods disclosed herein are particularly advantageous in that they are capable of editing a PAH gene in a cell with high efficiency both in vivo and in vitro. In certain embodiments, the integration efficiency of the editing element into the target locus is at least 1% (e.g., at least 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions. In certain embodiments, the allelic frequency of integration of the editing element into the target locus is at least 0.5% (e.g., at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 3%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) when the AAV is administered to a mouse implanted with human hepatocytes in the absence of an exogenous nuclease under standard AAV administration conditions.

The methods disclosed herein can be performed in vitro for research purposes or can be performed ex vivo or in vivo for therapeutic purposes.

In certain embodiments, the cell to be transduced is in a mammalian subject and the AAV is administered to the subject in an amount effective to transduce the cell in the subject. Accordingly, in certain embodiments, the instant disclosure provides a method for treating a subject having a disease or disorder associated with a PAH gene mutation, the method generally comprising administering to the subject an effective amount of an rAAV as disclosed herein. The subject can be a human subject, a non-human primate subject (e.g., a cynomolgus), or a rodent subject (e.g., a mouse) with a PAH gene mutation. Any disease or disorder associated with a PAH gene mutation can be treated using the methods disclosed herein. Suitable diseases or disorders include, without limitation, phenylketonuria (PKU).

In certain embodiments, the foregoing methods employ an rAAV comprising: (a) an AAV capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 16, and an rAAV genome comprising 5' to 3' following genetic elements: a 5' homology arm (e.g., the 5' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 23), a 5' ITR (e.g., the 5' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 14), a transcriptional regulatory element (e.g., a TRE comprising the nucleotide sequence set forth in SEQ ID NO: 27), an intron element (e.g., the intron element comprising the nucleotide sequence set forth in SEQ ID NO: 29), at least a portion of a PAH coding sequence (e.g., the PAH coding sequence comprising the nucleotide sequence set forth in SEQ ID NO: 28), a polyadenylation sequence (e.g., the SV40 polyadenylation sequence of SEQ ID NO: 31), a 3' ITR (e.g., the 3' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 18), and a 3' homology arm (e.g., the 3' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 24); (b) an AAV capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 16, and an rAAV genome comprising 5' to 3' following genetic elements: a 5' homology arm (e.g., the 5' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 23), a 5' ITR (e.g., the 5' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 14), a transcriptional regulatory element (e.g., a TRE comprising the nucleotide sequence set forth in SEQ ID NO: 27), an intron element (e.g., the intron element comprising the nucleotide sequence set forth in SEQ ID NO: 29), at least a portion of a PAH coding sequence (e.g., the PAH coding sequence comprising the nucleotide sequence set forth in SEQ ID NO: 28), a polyadenylation sequence (e.g., the SV40 polyadenylation sequence of SEQ ID NO: 31), a 3' ITR (e.g., the 3' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 18), and a 3' homology arm (e.g., the 3' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 24); and/or (c) an AAV capsid protein comprising the amino acid sequence of SEQ ID NO: 16, and an rAAV genome comprising 5' to 3' following genetic elements: a 5' homology arm (e.g., the 5' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 23), a 5' ITR (e.g., the 5' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 14), a transcriptional regulatory element (e.g., a TRE comprising the nucleotide sequence set forth in SEQ ID NO: 27), an intron element (e.g., the intron element comprising the nucleotide sequence set forth in SEQ ID NO: 29), at least a portion of a PAH coding sequence (e.g., the PAH coding sequence comprising the nucleotide sequence set forth in SEQ ID NO: 28), a polyadenylation sequence (e.g., the SV40 polyadenylation sequence of SEQ ID NO: 31), a 3' ITR (e.g., the 3' ITR comprising the nucleotide sequence set forth in SEQ ID NO: 18), and a 3' homology arm (e.g., the 3' homology arm comprising the nucleotide sequence set forth in SEQ ID NO: 24).

In certain embodiments, transduction of a cell with an AAV composition disclosed herein can be performed as provided herein or by any method of transduction known to one of ordinary skill in the art. In certain embodiments, the cell may be contacted with the AAV at a multiplicity of infection (MOI) of 50,000; 100,000; 150,000; 200,000; 250,000; 300,000; 350,000; 400,000; 450,000; or 500,000, or at any MOI that provides for optimal transduction of the cell.

An AAV composition disclosed herein can be administered to a subject by any appropriate route including, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, intranasal, topical or intradermal routes. In certain embodiments, the composition is formulated for administration via intravenous injection or subcutaneous injection.

IV. AAV PACKAGING SYSTEMS

In another aspect, the instant disclosure provides packaging systems for recombinant preparation of a recombinant adeno-associated virus (rAAV) disclosed herein. Such packaging systems generally comprise: first nucleotide encoding one or more AAV Rep proteins; a second nucleotide encoding a capsid protein of any of the AAVs as disclosed herein; and a third nucleotide sequence comprising any of the rAAV genomes as disclosed herein, wherein the packaging system is operative in a cell for enclosing the rAAV genome in the capsid to form the AAV.

In certain embodiments, the packaging system comprises a first vector comprising the first nucleotide sequence encoding the one or more AAV Rep proteins and the second nucleotide sequence encoding the AAV capsid protein, and a second vector comprising the third nucleotide sequence comprising the rAAV genome. As used in the context of a packaging system as described herein, a "vector" refers to a nucleic acid molecule that is a vehicle for introducing nucleic acids into a cell (e.g., a plasmid, a virus, a cosmid, an artificial chromosome, etc.).

Any AAV Rep protein can be employed in the packaging systems disclosed herein. In certain embodiments of the packaging system, the Rep nucleotide sequence encodes an AAV2 Rep protein. Suitable AAV2 Rep proteins include, without limitation, Rep 78/68 or Rep 68/52. In certain embodiments of the packaging system, the nucleotide sequence encoding the AAV2 Rep protein comprises a nucleotide sequence that encodes a protein having a minimum percent sequence identity to the AAV2 Rep amino acid sequence of SEQ ID NO: 22, wherein the minimum percent sequence identity is at least 70% (e.g., at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%) across the length of the amino acid sequence of the AAV2 Rep protein. In certain embodiments of the packaging system, the AAV2 Rep protein has the amino acid sequence set forth in SEQ ID NO: 22.

In certain embodiments of the packaging system, the packaging system further comprises a fourth nucleotide sequence comprising one or more helper virus genes. In certain embodiments of the packaging system, the packaging system further comprises a third vector, e.g., a helper virus vector, comprising the fourth nucleotide sequence comprising the one or more helper virus genes. The third vector may be an independent third vector, integral with the first vector, or integral with the second vector.

In certain embodiments of the packaging system, the helper virus is selected from the group consisting of adenovirus, herpes virus (including herpes simplex virus (HSV)), poxvirus (such as vaccinia virus), cytomegalovirus (CMV), and baculovirus. In certain embodiments of the packaging system, where the helper virus is adenovirus, the adenovirus genome comprises one or more adenovirus RNA genes selected from the group consisting of E1, E2, E4 and VA. In certain embodiments of the packaging system, where the helper virus is HSV, the HSV genome comprises one or more of HSV genes selected from the group consisting of UL5/8/52, ICPO, ICP4, ICP22 and UL30/UL42.

In certain embodiments of the packaging system, the first, second, and/or third vector are contained within one or more plasmids. In certain embodiments, the first vector and the third vector are contained within a first plasmid. In certain embodiments the second vector and the third vector are contained within a second plasmid.

In certain embodiments of the packaging system, the first, second, and/or third vector are contained within one or more recombinant helper viruses. In certain embodiments, the first vector and the third vector are contained within a recombinant helper virus. In certain embodiments, the second vector and the third vector are contained within a recombinant helper virus.

In a further aspect, the disclosure provides a method for recombinant preparation of an AAV as described herein, wherein the method comprises transfecting or transducing a cell with a packaging system as described herein under conditions operative for enclosing the rAAV genome in the capsid to form the rAAV as described herein. Exemplary methods for recombinant preparation of an rAAV include transient transfection (e.g., with one or more transfection plasmids containing a first, and a second, and optionally a third vector as described herein), viral infection (e.g., with one or more recombinant helper viruses, such as a adenovirus, poxvirus (such as vaccinia virus), herpes virus (including HSV, cytomegalovirus, or baculovirus), containing a first, and a second, and optionally a third vector as described herein), and stable producer cell line transfection or infection (e.g., with a stable producer cell, such as a mammalian or insect cell, containing a Rep nucleotide sequence encoding one or more AAV Rep proteins and/or a Cap nucleotide sequence encoding one or more AAV capsid proteins as described herein, and with an rAAV genome as described herein being delivered in the form of a plasmid or a recombinant helper virus).

Accordingly, the instant disclosure provides a packaging system for preparation of a recombinant AAV (rAAV), wherein the packaging system comprises a first nucleotide sequence encoding one or more AAV Rep proteins; a second nucleotide sequence encoding a capsid protein of any one of the AAVs described herein; a third nucleotide sequence comprising an rAAV genome sequence of any one of the AAVs described herein; and optionally a fourth nucleotide sequence comprising one or more helper virus genes.

V. EXAMPLES

These examples are offered by way of illustration, and not by way of limitation.

Example 1: hPAH Correction Vector Designs

Mouse-Specific PAH Gene Editing Vector PAH-006m

The mouse-specific gene editing AAV vector, PAH-006m, is shown in FIG. 2A. This vector was designed to integrate a human PAH coding sequence into the mouse PAH gene locus using left and right homology arms that are specific to the mouse sequence. PAH-006m comprises, from 5' to 3', the following genetic elements: a 5' ITR element; a 5' homology arm; a silently altered human PAH coding sequence; an SV40 polyadenylation sequence; a 3' homology arm; and a 3' ITR element. The sequences of these elements are set forth in Table 1. PAH-006m does not comprise a heterologous promoter.

Mouse-Specific PAH Gene Transfer Gene Editing Vector PAH-006m-LP-1

The mouse-specific gene transfer/gene editing AAV vector, PAH-006m-LP-1, is shown in FIG. 2B. This vector was designed to integrate a human PAH coding sequence into the mouse PAH gene locus using mouse left and right homology arms, and also to allow expression of human PAH under the control of a heterologous liver-specific promoter in a cell in the absence of genomic integration. PAH-006m-LP-1 comprises, from 5' to 3', the following genetic elements: a 5' ITR element; a 5' homology arm; a transcriptional regulatory element comprising a human apolipoprotein hepatic control region (HCR) element, a human alpha-1-antitrypsin (hAAT) promoter element, and a hAAT exon 1; an SV40 element; a silently altered human PAH coding sequence; an SV40 polyadenylation sequence; a 3' homology arm; and a 3' ITR element. The sequences of these elements are set forth in Table 1.

Human-Specific PAH Gene Editing Vector PAH-032h

The human-specific gene editing AAV vector, PAH-032h, is shown in FIG. 2C. This vector was designed to integrate a human PAH coding sequence into the human PAH gene locus using left and right homology arms that are specific to the human sequence. PAH-032h comprises, from 5' to 3', the following genetic elements: a 5' ITR element; a 5' homology arm; a splice acceptor; a 2A element; a silently altered human PAH coding sequence; an SV40 polyadenylation sequence; a 3' homology arm; and a 3' ITR element. The sequences of these elements are set forth in Table 1. PAH-032h does not comprise a heterologous promoter.

Human-Specific PAH Gene Transfer Gene Editing Vector hPAH-hI1C-032-LP1-SD3

The human-specific gene transfer/gene editing AAV vector, hPAH-hI1C-032-LP1-SD3, is shown in FIG. 2D. This vector was designed to integrate a human PAH coding sequence into the human PAH gene locus using human left and right homology arms, and also to allow expression of human PAH under the control of a heterologous liver-specific promoter in a cell in the absence of genomic integration. hPAH-hI1C-032-LP1-SD3 comprises, from 5' to 3', the following genetic elements: a 5' ITR element; a 5' homology arm; a transcriptional regulatory element comprising a human apolipoprotein hepatic control region (HCR) element, a human alpha-1-antitrypsin (hAAT) promoter element, and a hAAT exon 1; an SV40 element; a silently altered human PAH coding sequence; an SV40 polyadenylation sequence; a 3' homology arm; and a 3' ITR element. The sequences of these elements are set forth in Table 1.

TABLE 1

Selected genetic elements in PAH correction vectors PAH-006m, PAH-006m-LP-1, PAH-032h, and hPAH-hI1C-032-LP1-5D3

	PAH-006m	PAH-006m-LP-1	PAH-032h	hPAH-hI1C-032-LP1-5D3
Genetic Element	SEQ ID NO:			
5' ITR element	14	14	14	14
5' homology arm	84	85	23	23
Splice acceptor	—	—	30	—
2A element	—	—	40	—
transcriptional regulatory element	—	27	—	27
SV40 intron element	—	29	—	29
silently altered human PAH coding sequence	83	28	83	28
SV40 polyadenylation sequence	31	31	31	31
3' homology arm	86	86	24	24
3' ITR element	18	18	18	18

TABLE 1-continued

Selected genetic elements in PAH correction vectors PAH-006m, PAH-006m-LP-1, PAH-032h, and hPAH-hI1C-032-LP1-5D3

Genetic Element	PAH-006m	PAH-006m-LP-1	PAH-032h	hPAH-hI1C-032-LP1-5D3
	SEQ ID NO:			
AAV genome from 5' homology arm to 3' homology arm	77	79	81	43
AAV genome from 5' ITR to 3' ITR	78	80	82	45

"—" signifies an absence of this element

Example 2: Analysis of hPAH Correction Vectors in Mouse Models

Materials and Methods

PAH^{enu2} Mouse Model:

The PAH^{enu2} mouse model was used to establish dose response for PAH correction vectors packaged in AAVHSC15 capsid through measurement of vector genomes, percent target gene insertion, hPAH mRNA expression, and Phe/Tyr concentration.

The PAH^{enu2} mouse line was produced by germline ethylnitrosourea mutagenesis followed by a Phe clearance screen to isolate a mutant mouse line deficient in PAH activity (see McDonald J D, et al. *PNAS* 1990; 87:1965-1967, which is hereby incorporated by reference in its entirety). It has a homozygous missense mutation (F263S in exon 7) in the region encoding the PAH active site, resulting in abolished activity of PAH. Mutations within exon 7 are common in humans with PAH deficiency, although PAH deficiency in humans is typically expressed in a compound heterozygous background. PAH^{enu2} mice exhibit present with blood Phe levels consistently above 1200 μmol/L.

FRG® Mouse Human Liver Xenograft Model:

Fah$^{-/-}$/Rag2$^{-/-}$/Il2rg$^{-/-}$ (FRG) mice (Azuma et al. (2007) *Nat. Biotechnol.* 25(8): 903-910) containing human liver tissue were used to measure in vivo transduction of vector genomes, human DNA target gene insertion, and mRNA expression of hPAH in human liver tissue, following administration of correction vectors packaged in AAVHSC15 capsid across a range of doses.

The FRG® human liver xenograft model is an immunocompromised mouse strain harboring triple gene knockouts of Fah$^{-/-}$, IL2rg$^{-/-}$ and Rag2$^{-/-}$. Because of the IL2rg$^{-/-}$ and Rag2$^{-/-}$ knockouts these mice lack B-cell, T-cell and NK-cells resulting in acceptance of engraftment with human cells. The Fah$^{-/-}$ genotype renders these mice dependent on the liver protective drug, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), such that its withdrawal leads to loss of hepatocytes and animal death within 4-8 weeks.

To generate humanized livers in FRG mice, human primary hepatocytes were implanted concurrent with NTBC withdrawal. Since the human hepatocytes have an intact FAH gene, only murine hepatocytes are affected, resulting in the gradual repopulation of the mouse liver compartment with human hepatocytes. The human repopulated livers show >90% human hepatocytes and restored hepatic function (Azuma et al. (2007) *Nat. Biotechnol.* 25(8): 903-910).

On-Target Insertion—ddPCR Linkage Assay:

To determine the level of target insertion per allele at the PAH gene locus, an assay that uses droplet digital PCR (ddPCR) was employed. In this assay, target insertion was determined by measuring genetic linkage between the hPAH transgene and the genomic target. Linkage is a measurement of how often two sequences are on the same strand of DNA. Determining the amount of linked to unlinked vector and genome sequences can be used to measure insertion efficiency, which is reported as percent insertion per allele.

To measure target insertion via linkage, two primer and probe sets were used, one targeting the silently altered hPAH payload and a second targeting the Pah genomic sequence beyond the homology arms. Each probe consisted of a fluorophore in either the FAM or HEX channel such that when DNA is analyzed in partitioned droplets, each droplet can be scored by its emission signature as producing one of three possible signals: FAM-positive (silently altered hPAH payload alone); HEX-positive (genomic alone); and HEX+FAM positive (contains silently altered hPAH payload and genomic sequence). Target insertion was measured by determining the proportion of droplets containing both the payload and the genomic sequence in excess of expectation due to probability, divided by the total number of Pah alleles tested.

As the relative concentration of vector to genome can vary across doses and models, it is important to ensure each measurement is within the linear range of detection for both the vector and the target genomic sequence. Therefore, prior to measuring target insertion, the relative abundance of vector and target genome was measured across a range of sample input concentrations from 1 ng, 5 ng, 10 ng, 100 ng. The ratio of vector to genome was used to determine the sample input concentration in which both the vector and genomes fall within the limits of detection by ddPCR which are between 0.25-5000 molecules per μl.

On-Target Insertion—Next Generation Sequencing (NGS) Assay:

This approach was used to calculate target insertion using assays spanning both left and right integration sites of the human PAH editing construct. Each of the two amplicons share their respective outward primer located on the genomic DNA flanking each homology arm, while the inward primers were unique for unedited alleles or for the edited alleles respectively. Each number of wild-type (WT) and edited sequences were tallied by counting the number of sequences covering the junction between the homology arm and either the inserted gene or the unedited wild-type sequence. Having separate assays covering both the left and right side of the insertion site provides redundant quantitation of insertion. By using this NGS approach, the percentage of target insertions can be detected per total number of alleles, and in addition, sequences of the entire insertion site can be collected, enabling the detection of de novo mutations (e.g., incorrect insertion and deletion events and ITR integration).

Differences of uninserted and inserted amplification efficiency were accounted for using an 11-step standard for both left and right integration sites. Each control panel consists of purified uninserted amplicon and edited amplicon at the following ratios: 0% edited, 1%, 2%, 5%, 10% 50%, 60%, 90%, 95%, 98%, 99% and 100% edited control sequence. Target insertion efficiency calculations were as follows: the sequencing reads specific to uninserted and inserted genomic loci are tallied and target insertion was calculated by (insertion read counts/total read counts*100%) and fitted to the standard curve. As editing quantitation per sample was measured by two independent assays, each spanning opposite homology arms into the native genome, the consistency between each measurement was determined.

On-Target Accuracy—Next Generation Sequencing (NGS) Assay:

To determine if target gene insertion is accompanied by de novo mutation at the integration sites, PCR amplicons spanning genomic sequences beyond both left and right of the homologous arms and into the target insertion site were sequenced. A total of four amplicons were sequenced per sample. Insertion specific amplicons spanning each homology arm (hPAH dependent PCR) or WT/uninserted alleles spanning each homology arm (no hPAH insertion) were assessed.

To identify the detection limit of the assay, an amplicon-based control panel was built by mixing two right homologous arm amplicons, varied by one base (a T to G variation), at 0%, 0.1%, 0.5%, 1%, 2%, 5%, 10%, 50, and 100%. The amplicon control panel went through the same processing steps. Based on the quantitative variant calling from the standard curve, false-positive variants were observed at a frequency of 0.1-0.25% at non-random positions. Sequencing coverage for almost all positions was above 10,000. A variant was considered to be a true positive with the following criteria: (1) at >0.5% variant frequency and pass filters; (2) appear in both technical sequencing duplicates; and (3) not observed in WT alleles given comparable sequence depth and quality.

Results

A study was performed in PAH^{enu2} mice using the mouse-specific correction vector, PAH-006m, which contains homology arms targeting the mouse PAH locus. PAH-006m does not contain a liver specific promoter, and as such, expression is driven by the endogenous promoter elements. Three male mice per group were administered either 1E+14 vg/kg PAH-006m packaged in AAVHSC15 capsid, or formulation buffer, and blood Phe level was measured weekly for 12 weeks. At the 12-week timepoint, mice were sacrificed to measure target insertion at the PAH locus, and mRNA expression levels.

Blood Phe levels were reduced to normal levels by 2 weeks post-administration of PAH-006m packaged in AAVHSC15 capsid, as shown in FIG. **3**. Reduction of blood Phe was maintained at levels of <360 μM for the duration of the 12-week study.

The level of on-target insertion at the PAH locus was measured using the ddPCR linkage assay as described in the Materials and Methods above. A range of 3-7% target insertion per allele was detected in the liver at the 12-week timepoint, as shown in FIG. **4**. The level of silently altered hPAH mRNA was also measured (relative to mouse GAPDH) and is shown in FIG. **5**. The expression of silently altered hPAH mRNA was detected (PAH/GAPDH mRNA ratio was 0.38±0.06). Of note, the level of on-target insertion per allele was found to be directly correlated to the level of mRNA expression (R-squared 0.82; P<0.02).

To determine if similar levels of on-target insertion and mRNA expression could be achieved in human liver, experiments were conducted in the FRG® mouse containing a human liver xenograft. Mice were treated with a single IV dose of 1E+14 vg/kg PAH-032h packaged in AAVHSC15 capsid. PAH-032h does not contain the liver specific promoter, and as such, expression is driven by the endogenous human promoter elements, similar to construct PAH-006m.

Expression of hPAH mRNA derived from silently altered hPAH was evaluated in liver cells from the FRG® mouse. Expression was measured by RT-ddPCR and expressed as a ratio to GAPDH to allow for comparison across human and mouse hepatocytes. In the human hepatocytes isolated from the FRG® mouse model, 6-weeks after administration of PAH-032h packaged in AAVHSC15 capsid, hPAH mRNA derived from silently altered hPAH was expressed (hPAH/GAPDH mRNA ratio=0.57±0.11). Levels of silently altered hPAH mRNA in mouse hepatocytes were significantly lower (PAH/GAPDH mRNA ratio=0.13±0.08, p<0.003 vs human) and could be entirely accounted for by the presence of contaminating human hepatocytes in the preparations used (approximately 15-20% human). The proportion of mouse cells in human samples and human cells in mouse samples was calculated by measuring the relative abundance of human and mouse GAPDH gene in each sample.

Confirmation of human-specific target insertion into the human PAH locus was done in a separate study in FRG® mice where levels of on-target insertion (~6% using the linkage ddPCR method; FIG. **6**) and levels of hPAH mRNA derived from silently altered hPAH (hPAH/GAPDH mRNA ratio=0.45±0.26) were achieved in human cells with treatment of PAH-032h packaged in AAVHSC15 capsid. Target gene insertion efficiency was characterized using the NGS assay in which quantitation of integration is based on two separate measurements that cover both the left and right homology arms, respectively, with coverage extending into the genomic targeted integration sites and past the end of each homology arm, as described in the Materials and Methods above. Untreated wild-type genomic DNA was used to detect the false-positive rate for this experiment. Integration of hPAH into the PAH locus was confirmed with orthogonal assays (linkage ddPCR and NGS) reporting integration efficiencies of 6%. These results are shown in FIG. **7**.

FIG. **6** and FIG. **7** show targeted insertion frequency in hepatocytes isolated from treated FRG mice. FIG. **6** shows insertion of the human-targeting PAH-032h correction vector packaged in AAVHSC15 capsid into mouse and human PAH loci, as measured by the species specific ddPCR editing assays described herein. As a positive control linkage between a mouse-specific PAH locus probe and a probe for the homologous insertion site was used. In FIG. **6**, An.1 HS refers to Animal 1 *Homo sapiens* Cells, An.1 MM refers to Animal 1 *Mus musculus* cells, An.1 MM Pos. refers to Animal 1 *Mus musculus* positive control, An.2 HS refers to Animal 2 *Homo sapiens* Cells, An.2 MM refers to Animal 2 *Mus musculus* cells, and An.2 MM Pos. refers to Animal 2 *Mus musculus* positive control. FIG. **7** shows the editing of human hepatocytes as measured by quantitative NGS assays spanning both left and right homology arms. Editing efficiency was measured by read counts of edits specific to wild-type specific sequences. Untreated human DNA mixed with PAH-032h vector served as a negative control.

From these studies, it can be concluded that: (1) blood Phe concentration is reduced to a therapeutically relevant threshold (≤360 μM) following administration of the mouse construct PAH-006m packaged in AAVHSC15 capsid into PAH^{enu2} mice; (2) similar levels of mRNA expression were observed across species between the mouse-specific construct PAH-006m in PAH^{enu2} mice and the human specific construct PAH-032h in the human liver tissue of FRG® mice, both packaged in AAVHSC15 capsid; (3) no significant target insertion was observed in mouse hepatocytes (using mouse-specific assays) following administration of the human specific construct PAH-032h packaged in AAVHSC15 capsid into FRG® mice, demonstrating the sequence/species specificity of the human homology arms; and (4) similar levels of on-target integration per allele were achieved across species between the mouse-specific construct PAH-006m in the PAH^{enu2} mouse (4-7%) and the human specific construct PAH-032h in the FRG mouse (~6%).

Example 3: In Vivo Efficacy of PAH-006m-LP-1 in PAH^{enu2} Mice

The ability of the PAH-006m-LP-1 vector to reduce blood Phe levels in mice was assessed and correlated with hPAH mRNA expression and target insertion at the mouse PAH locus. Specifically, four PAH^{enu2} mice received single intravenous administration of the murine specific PAH-006m-LP-1 vector packaged in AAVHSC15 capsid covering a ~2-log dose range, with dose levels of 5E+12, 1E+13, 1E+14, and 2E+14 vg/kg ("GE 5E12," "GE 1E13," "GE 1E14," and "GE 2E14," respectively). In addition, a control arm containing an AAV gene transfer construct expressing hPAH but with no homology arms was administered at a dose of 1E+13 vg/kg ("GT (+) control 1E13"). Four PAH^{enu2} mice were also administered formulation buffer as a negative control ("FB"). Blood Phe concentration was measured over the course of the experiment.

A subset of animals dosed at 1E+14 vg/kg were sacrificed at the 2-week timepoint to measure the level of target gene insertion in the liver. A level of 5±2% target gene insertion per allele was detected. The blood Phe concentrations in the mice through week 41 are shown in FIG. **8**A. FIG. **8**A shows the full data set, while FIG. **8**B shows the data out to 12 weeks with a reduced y-axis scale to allow differences between the dose levels to be seen more clearly. Blood Phe concentration was reduced to normal levels by one week following administration of all dose levels, with the 1E+14 and 2E+14 doses resulting in the lowest levels.

On-target analysis was performed on animals dosed at 5E12 vg/kg ("5E+12"), 1E13 vg/kg ("1E+13"), and 1E14 vg/kg ("1E+14"), as indicated (FIG. **8**C). On-target integration was measured by next generation sequencing as described in Example 2. Integration rates were calculated based on the number of sequences with the integration divided by total number of sequences (with or without the integration event). In FIG. **8**C, all data was collected at 43 weeks post-dosing, except "1E+14 vg/kg—3 wks" where the data was collected at 3 weeks post-dosing. As shown, on-target integration was detected in animals dosed with 1E14 vg/kg PAH-006m-LP-1 vector packaged in AAVHSC15 capsid at both 3 and 43 weeks post-dosing.

Example 4: In Vitro Editing Specificity of PAH-032h in Non-Human Primate and Human Hepatocytes

Cynomolgus monkeys exhibit 94.2% sequence identity at the PAH locus to the human homology arm sequences of PAH-032h. To determine the specificity of PAH-032h for the human PAH locus, the ability of PAH-032h to edit the PAH locus in a mixture of primary cynomolgus monkey and primary human hepatocytes was assessed. A total of 5E+5 hepatocytes from a single cynomolgus monkey and a single human donor were treated with 1.5E+5 vg/cell of PAH-032h vector packaged in an AAVHSC15 capsid. Editing of the PAH locus was assessed by PCR using primers specific for the human edited allele and primers specific for the non-human primate edited allele. These PCR primers were designed to show either presence or absence of integration and were not quantitative. Accordingly, measurements of PCR efficiency were determined in positive control DNA across a standard curve of dilutions. This PCR assay had a lower limit of detection of 15 copies of edited allele (2.618E-5 amol).

Targeted integration of the payload into the PAH locus of human hepatocytes was observed. In contrast, no integration of the payload into the homologous cynomolgus monkey loci was detected. These results indicate that the human homology arms were specific for the human PAH locus in these assays.

Example 5: Comparison Between Gene Transfer/Gene Editing Vector and Episomal Transgene Expression Vector

To investigate the dose response of integrated transgene expression and episomal transgene expression, a head-to-head comparison was performed using the mouse-specific gene transfer/gene editing AAV vector, PAH-006m-LP-1, and an episomal transgene expression AAV vector (containing the same transcriptional regulatory element as PAH-006m-LP-1, but lacking homology arms), packaged in AAVHSC15 capsid. The only difference between the payloads of the two vectors was the presence of two silent nucleotide changes in the PAH coding sequence of PAH-006m-LP-1. Five male, 4-week-old PAH^{enu2} mice were intravenously administered 1E12 vg/kg ("1E+12"), 5E12 vg/kg ("5E+12"), 1E13 vg/kg ("1E+13"), 5E13 vg/kg ("5E+13"), or 1E14 vg/kg ("1E+14") doses of either the mouse-specific gene transfer/gene editing vector or the episomal transgene expression vector, in each case packaged in AAVHSC15, or a formulation buffer control (FB). For the episomal transgene expression vector packaged in AAVHSC15, after an official titering procedure, the titer of the lot used was accordingly adjusted to 7.8E11 vg/kg ("7.8E+11"), 3.9E12 vg/kg ("3.9E+12 vg/kg"), 7.8E12 vg/kg ("7.8E+12"), 3.9E13 vg/kg ("3.9E+13"), and 7.8E13 vg/kg ("7.8E+13"). It was found that targeted integration in mice dosed with PAH-006m-LP-1 was detectible and stable. A dose response between phenotype correction and levels of integration was also found.

FIGS. **9**A and **9**B show 12-week time courses of the serum Phe levels in the mice that were dosed as described above. As shown, a reduction in serum Phe was observed in mice that received the episomal transgene expression vector packaged in AAVHSC15 capsid (FIG. **9**A), or the gene transfer/gene editing vector packaged in AAVHSC15 capsid (FIG. **9**B). Corresponding increases in blood Tyr concentration, a downstream metabolite of Phe, were also observed in mice that received the episomal transgene expression vector packaged in AAVHSC15 capsid (FIG. **9**C), or the gene transfer/gene editing vector packaged in AAVHSC15 capsid (FIG. **9**D).

FIGS. **9**E and **9**F show the vector genome levels in PAH^{enu2} mice dosed with the episomal transgene expression vector (FIG. **9**E) or PAH-006m-LP1 (FIG. **9**F), in each case packaged in AAVHSC15 capsid, at the indicated doses. Vector genomes per ug of DNA were measured using quantitative PCR using a coding sequence specific primer and probes relative to input genomic DNA target. A dose response in both vector genome copy number and mRNA was observed for both PAH-006m-LP-1 and the episomal transgene expression vector. The vector copy number for PAH-006m-LP-1 (FIG. **9**F) was higher across all doses compared to the episomal transgene expression vector (FIG. **9**E). Differences in VG/ug between the transgene and the integration vector are observed and may reflect differences in stability between self-complementary and single-stranded vectors.

FIGS. **9**G and **9**H show the PAH transgene mRNA expression levels in PAH^{enu2} mice dosed with the episomal transgene expression vector (FIG. **9**G) or PAH-006m-LP1 (FIG. **9**H), in each case packaged in AAVHSC15 capsid, at the indicated doses. mRNA levels were measured by quantitative RT-PCR using coding sequence specific primers and probes relative to total RNA. As shown, mRNA expression was found to be dose-responsive, and expression level was found to be slightly higher in mice that received PAH-006m-LP-1 packaged in AAVHSC15 capsid as compared to mice that received the episomal transgene expression vector packaged in AAVHSC15 capsid.

To assess the quantity and fidelity of target locus integration in PAH^{enu2} mice, two methods were performed to detect integration events: ddPCR and next generation sequencing.

The level of on-target integration at the PAH locus was measured using the ddPCR linkage assay as described in Example 2. FIG. **9**I shows the amount of on-target integration (measured in viral genomes per PAH allele detected by ddPCR) at 12 weeks post-dosing for the various doses of PAH-006m-LP1 and episomal transgene expression vector control indicated. As shown, a dose response of targeted integration detected by ddPCR was observed in mice that received PAH-006m-LP1 packaged in AAVHSC15 capsid (FIG. **9**I; Groups 2, 3, 4, 5, and 6). In comparison, no targeted integration was detected by ddPCR in mice that received the episomal transgene expression vector packaged in AAVHSC15 capsid (FIG. **9**I; Group 11).

FIG. **9**J shows the frequency of on-target vector insertion detected (using the NGS approach described in Example 2) 12 weeks post-dosing with the indicated doses of PAH-006m-LP1 packaged in AAVHSC15. As shown, a dose response of targeted integration detected by NGS was observed in mice that received PAH-006m-LP1 packaged in AAVHSC15 capsid. In comparison, no targeted integration was detected by NGS in mice that received the episomal transgene expression vector packaged in AAVHSC15 capsid. Integration level was found to be dose-responsive and higher than 2% at doses greater than 5E13 vg/kg.

To evaluate the effect of integrated transgene expression and episomal transgene expression in proliferating cell populations, 10-week-old PAH^{enu2} mice were intravenously administered 5E12 vg/kg, 2E13 vg/kg, 6E13 vg/kg, or 1E15 vg/kg doses of either the mouse-specific gene transfer/gene editing vector or the episomal transgene expression vector, in each case packaged in AAVHSC15, or a formulation buffer control (FB). For the episomal transgene expression vector packaged in AAVHSC15, after an official titering procedure, the titer of the lot used was accordingly adjusted to 3.92E12 vg/kg ("3.92E+12"), 1.57E13 vg/kg ("1.57E+13 vg/kg"), 4.71E13 vg/kg ("4.71E+13"), and 7.84E13 vg/kg ("7.84E+13"). About 2 weeks post-dosing, the mice underwent either a 70% partial hepatectomy (PHx) to induce rapid hepatocyte cycling, or a sham surgery (sham). FIGS. **9**K and **9**L show a time course out to 42 weeks (FIG. **9**K) or 40 weeks (FIG. **9**L) of the serum Phe levels in these mice. As shown, in mice treated with the episomal transgene expression vector (FIG. **9**K), serum Phe levels were reduced at weeks 1 and 2. Following hepatectomy at the 2-week timepoint, the Phe levels at the 5E12 vg/kg and 2E13 vg/kg dose levels increased during the period of accelerated liver regeneration. The sham surgery animals treated with 2E13 vg/kg episomal transgene expression vector did not show a loss of this response, indicating that the increase in serum Phe levels in the episomal transgene expression vector treated hepatectomized mice may be due to vector dilution under conditions of accelerated liver growth that occurred following hepatectomy. Mice treated with the gene transfer/gene editing vector (FIG. **9**L) showed a stable reduction in Phe levels throughout the period of accelerated liver growth in the partially hepatectomized mice. This result may be indicative of the benefit of integration at the target mouse Pah locus.

Example 6: Comparison Between Mouse-Specific Vector and Human-Specific Vector

To investigate dose range differences between the mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1; "mouse design"), and the human-specific gene transfer/gene editing AAV vector (hPAH-hI1C-032-LP1-SD3; "human design") was used in a head-to-head study. Four to five male, 4-week-old (FIGS. **10**A-**10**H) or 10-week-old (FIGS. **10**I-**10**P) PAH^{enu2} mice were intravenously administered 1E12 vg/kg, 5E12 vg/kg, 1E13 vg/kg, or 5E13 vg/kg of either the mouse design vector (FIGS. **10**A, **10**C, **10**E, **10**G, **10**I, **10**K, **10**M, and **10**O) or the human design vector (FIGS. **10**B, **10**D, **10**F, **10**H, **10**J, **10**L, **10**N, and **10**P), in each case packaged in AAVHSC15, or a formulation buffer control (FB).

The human design vector comprises human homology arm sequences and would not be expected to integrate into the mouse genome via homologous recombination due to sequence differences, accordingly the human design vector served as an episomal-only control in these experiments. As shown, 4-week-old mice dosed with the human design vector packaged in AAVHSC15 capsid (FIG. **10**B) exhibited an improvement in serum Phe reduction, similar to mice administered the mouse design vector (FIG. **10**A). A corresponding increase in blood Tyr concentration was also observed in the 4-week-old mice dosed with the human design vector packaged in AAVHSC15 capsid (FIG. **10**D) and in the mice dosed with the mouse design vector (FIG. **10**C). As shown in FIGS. **10**E and **10**F, a dose response was observed for vector genome levels detected in the liver of 4-week-old mice dosed with the human design vector (FIG. **10**F) or the mouse design vector (FIG. **10**E) packaged in AAVHSC15 capsid. A dose response was also observed for mRNA levels detected in the liver of 4-week-old mice dosed with the human design vector (FIG. **10**H) or the mouse design vector (FIG. **10**G) packaged in AAVHSC15 capsid.

At 10 weeks old, mice dosed with the human design vector packaged in AAVHSC15 capsid (FIG. **10**I) were found to have a similar reduction in serum Phe levels, compared to mice dosed with the mouse design vector (FIG. **10**H). A corresponding increase in blood Tyr concentration was also observed in the 10-week-old mice dosed with the human design vector packaged in AAVHSC15 capsid (FIG. **10**K) and in mice dosed with the mouse design vector (FIG. **10**J). As shown in FIGS. **10**M and ION, a dose response was observed for vector genome levels detected in the liver of 10-week-old mice dosed with the human design vector (FIG. **10**N) or the mouse design vector (FIG. **10**M) packaged in AAVHSC15 capsid. A dose response was also observed for mRNA levels detected in the liver of 10-week-old mice dosed with the human design vector (FIG. **10**P) or the mouse design vector (FIG. **10**O) packaged in AAVHSC15 capsid.

Example 7: Effect of a Single Dose of Mouse-Specific Vector or Human-Specific Vector

To evaluate the effect of the age of PAHenu2 mice on the response to a single dose of the mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1; "mouse design") or the human-specific gene transfer/gene editing AAV vector (hPAH-hI1C-032-LP1-SD3; "human design"), mice at 2-, 4-, and 10-weeks of age were selected. This allowed for a comparison between the effect of pediatric liver growth (2- and 4-week-old mice) and the liver of an adult (10-week-old mice). A single 1E14 vg/kg dose of the mouse design vector packaged in AAVHSC15 or the human design vector packaged in AAVHSC15 was intravenously administered to PAHenu2 mice at 2-, 4-, or 10-weeks of age. A total of four to five male mice in each age group were administered the respective packaged vectors. Formulation buffer was administered as control. As the human design vector does not integrate into the mouse Pah locus, it provides a control to demonstrate the effect of episomal expression on mice of different ages. In this example, after an official titering procedure, the titer of the lot used was accordingly adjusted to 9.07E13 vg/kg for the mouse design and 1.06E14 vg/kg for the human design. The various dosing cohorts studied are set forth in Table 2.

TABLE 2

Dosing Cohorts				
Group	Test Article	Dose Level (vg/kg)	Number of mice dosed/Sex (age at dosing)	Necropsy (weeks post-administration)
1	Formulation buffer	NA	5/M (2-weeks)	43 weeks
2	Mouse design vector packaged in AAVHSC15	1E + 14 (9.07E13)	5/M (2-weeks)	
3			4/M (4-weeks)	
4			4/M (10-weeks)	
5			4/M (2-weeks)	2 weeks
6			4/M (2-weeks)	4 weeks
7			4/M (2-weeks)	8 weeks
8	Formulation buffer	NA	4/M (2-weeks)	42 weeks
9	Human design vector packaged in AAVHSC15	1E + 14 (1.06E14)	4/M (2-weeks)	
10			4/M (4-weeks)	
11			4/M (10-weeks)	
12			4/M (2-weeks)	2 weeks
13			4/M (2-weeks)	4 weeks
14			4/M (2-weeks)	8 weeks
15	Mouse design vector packaged in AAVHSC15		4/M (4-weeks)	42 weeks

As set forth in Table 2, Groups 1-4 were sacrificed 43 weeks post-administration, and Groups 8-11, and 15 were sacrificed 42 weeks post-administration. Serum Phe and Tyr levels were examined over time for Groups 1-4, 8-11, and 15 (FIGS. **11**A-**11**D). FIGS. **11**E-**11**K show the vector genome levels and mRNA levels detected in the livers of mice at the necropsy time points indicated in Table 2. mRNA levels in the livers of Groups 5-7 mice were not measured.

In mice treated with the mouse design vector, serum Phe levels were reduced to normal levels within one week following administration of the vector (FIG. **11**A). For the treated 4- and 10-week-old mice (Groups 3 and 4), the reduction in Phe levels was maintained through 43 weeks, demonstrating long term durability of response to treatment. For the 2-week-old mice, the results were variable. A corresponding increase in serum Tyr concentration was observed in the 4- and 10-week-old mice through 43 weeks (FIG. **11**C). FIG. **11**E shows the vector genome levels detected in the liver of 2-, 4-, and 10-week-old mice treated with the mouse design vector. FIG. **11**I shows the mRNA levels detected in the liver of 2-, 4-, and 10-week-old mice treated with the mouse design vector.

In mice treated with the human design vector, serum Phe levels were reduced by the one week time point following administration of the vector (FIG. **11**B). For the treated 4- and 10-week-old mice (Groups 10 and 11), the reduction in Phe levels was maintained through 43 weeks, indicating long term durability of response to treatment. In the treated 2-week-old mice (Group 9), Phe levels maintained at clinically relevant levels of ≤360 μM through 30 weeks. A corresponding increase in serum Tyr concentration was observed in Groups 9 (through 30 weeks), 10 (through 42 weeks), and 11 (through 42 weeks) (FIG. **11**D). These data indicate that a 1E14 vg/kg dose of the human design vector packaged in AAVHSC15 is sufficient to provide sustained efficacy through the period of liver growth in a juvenile mouse, and that the effect is sustained for at least 30 weeks post-administration. FIG. **11**F shows the vector genome levels detected in the liver of 2-, 4-, and 10-week-old mice treated with the human design vector. FIG. **11**J shows the mRNA levels detected in the liver of 2-, 4-, and 10-week-old mice treated with the human design vector.

FIGS. **11**G and **11**H show that in 2-week-old mice treated with the mouse design vector (FIG. **11**G; Groups 5-7) and 2-week-old mice treated with the human design vector (FIG. **11**H; Groups 12-14), vector genome levels were sustained up to 8 weeks post-administration. FIG. **11**K shows that mRNA levels of 2-week-old mice treated with the human design vector were sustained up to 8 weeks post-administration.

Example 8: Kinetics and Durability of Integration in Adult PAH^{enu2} Mice

To determine kinetics and durability of vector integration over time, 10-week-old male PAH^{enu2} mice were administered a mouse-specific gene transfer/gene editing AAV vector (PAH-006m-LP-1) packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg. Six cohorts were sacrificed at 1, 2, 4, 8, and 16 weeks post-dosing (five mice per cohort). The kinetics of integration was investigated by monitoring serum Phe levels over time, vector genome levels over time, PAH transgene mRNA expression levels over time, and targeted integration levels overtime, at the various time points. It was found that vector genome levels, PAH transgene mRNA expression levels, and integration frequencies were stable over time (FIGS. **12**A-**12**C).

FIGS. **12**A and **12**B show a time course of vector genome levels (FIG. **12**A) and PAH transgene mRNA expression levels (FIG. **12**B) in PAH^{enu2} mice administered PAH-006m-LP-1 packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg. The vector genome and the mRNA levels over time were found to be stable up to 42 weeks. Vector genome levels were measured using quantitative PCR using a coding sequence specific primer and probes relative to input genomic DNA target. Measurement of expression was performed by quantitative RT-PCR using coding sequence specific primers and probes relative to total RNA.

A long-read next generation sequencing (NGS) method was developed to quantitate integrated versus unintegrated alleles. Long-read sequencing was selected due to the length of the homology arms requiring a read through of the integration sequence and into the genomic DNA. The method was able to distinguish between integrated alleles, wild-type alleles, and vector genomes that are present in a given sample. PCR is performed using three primers specific to i) the genomic region; ii) a region specific to the integrated allele; and iii) a region specific to the wild-type allele. The frequency of on-target vector integration was determined by competitively amplifying both wild-type and integrated alleles at the PAH region using DNA derived from the livers of treated animals. The long-read sequencing of the amplified products covered the homology arm, which was identical across genomic, integrated, and vector genome sequences. The adjoining sequences, which were also covered by long-read sequencing, determine whether the source of the read was from wild-type, integrated, or vector genomes. Contiguous sequences that included both the genomic DNA and the silently altered hPAH transgene were tallied as integrated alleles, while sequences that included only the genomic DNA without the silently altered hPAH transgene in the target integration site were tallied as wild-type alleles. Percentage of integrated sequences were calculated as the number of reads mapped to the integrated reference divided by the total number of reads mapped to the integrated reference, reads mapped to the wild-type reference, and reads mapped to vector genome concatemers. FIG. **12**C shows a time course of targeted integration frequency in PAH^{enu2} mice administered PAH-006m-LP-1 packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg. On-target integration was detected at one week post-dosing, achieved peak levels by about 2 weeks, and remained consistent through 42 weeks.

FIGS. **12**D and **12**E are graphs showing the effect on serum Phe (FIG. **12**D) and Tyr (FIG. **12**E) in PAH^{enu2} mice administered PAH-006m-LP-1 packaged in AAVHSC15 capsid at a dose of 1E14 vg/kg, up to 42 weeks post-injection.

Example 9: In Vivo Efficacy of hPAH-hI1C-032-LP1-SD3

To determine kinetics and durability of integration of a human specific gene transfer/gene editing vector over time, male humanized liver FRG mice ("HuLiv" mice; see, Example 2) were administered the human-specific gene transfer/gene editing vector, hPAH-hI1C-032-LP1-SD3, packaged in AAVHSC15 capsid, at a dose of 7E13 vg/kg (Groups 1 and 3) or 2E14 vg/kg (Groups 2 and 4), and sacrificed at 4 (Groups 1 and 2) or 12 weeks (Groups 3 and 4) post-dosing (six male mice per cohort). Control FRG mice were administered formulation buffer and sacrificed at 4 (Group 5) or 12 weeks (Group 6) post-administration.

FIGS. **13**A and **13**B show the vector genome levels and mRNA levels detected in human hepatocytes isolated from HuLiv mice at 4 and 12 weeks after administration of hPAH-hI1C-032-LP1-SD3 packaged in AAVHSC15, at the indicated doses. As shown, the level of vector genomes (FIG. **13**A) and mRNA expression (FIG. **13**B) in human hepatocytes were found to be dose responsive and stable over time up to 12 weeks. Vector genome levels were measured using quantitative PCR using a coding sequence specific primer and probes relative to input genomic DNA target. Measurement of expression was performed by quantitative RT-PCR using coding sequence specific primers and probes relative to total RNA. FIG. **13**C shows the frequency of on-target integration detected in human hepatocytes isolated from HuLiv mice at 4 and 12 weeks after administration of hPAH-hI1C-032-LP1-SD3 packaged in AAVHSC15, at the indicated doses. As shown, the level of on-target integration in human hepatocytes was found to be dose responsive and stable over time up to 12 weeks. Measurement of targeted integration was carried out using the long-read NGS method described in Example 8.

Given that homologous recombination may be driven by short stretches of sequence similarity between the homology arms of the vector and an off-target location in the genome, a PCR-based assay was developed to specifically test for integration into genomic regions that contain sequence similar to the homology arms. The method bioinformatically predicted the most likely regions to undergo off-target homologous recombination in human cells transduced with vector containing homology arms specific to the human PAH locus. These predicted regions were selected based on the highest sequence similarity to the homology arms. A PCR-based method was designed to specifically test transduced samples for any occurrence of off-target integration in the predicted regions. Using this PCR-based method, integration to a level of 1:10000 DNA molecules was able to be detected.

Predicted off-target integration sites were selected based on two criteria: a minimum sequence length of 35 bp; and a minimum sequence identity of 60% relative to the homology arms. Six regions of the genome were identified that met these criteria via bioinformatic alignment against Genome Reference Consortium Human Build 38. PCR primers that allow specific amplification for off-target integration at 5 of these 6 regions were designed. Region 3 was found to be in a highly repetitive region and was dropped from further analysis because specific primers could not be generated. As positive controls ("Pos"), specific control DNAs spiked into genomic DNA, were run for each specific region down to a dilution of 1:10,000, representing 0.010% and the limit of detection of the PCR-based method. For each predicted region, integration-specific primer pairs targeting homologous recombination in either direction (inward ("In") or outward ("Out") from the region of homology) were tested independently to query for off-target integration. Off-target integration was defined as positive if a distinct PCR band of the correct size was identified in a sample.

FIGS. **14**A-**14**D show the results of predicted off-target integration determined by the PCR-based method described above, performed on genomic DNA samples isolated from 10-week-old male humanized liver FRG mice administered the human-specific gene transfer/gene editing vector, hPAH-hI1C-032-LP1-SD3, packaged in AAVHSC15 capsid, at a dose of 7E13 vg/kg (FIGS. **14**A and **14**C) or 2E14 vg/kg (FIGS. **14**B and **14**D), and sacrificed at 4 (FIGS. **14**A and **14**B) or 12 weeks (FIGS. **14**C and **14**D) post-dosing (six male mice per cohort). As shown, no integration was detected at the predicted off-target integration sites.

The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

All references (e.g., publications or patents or patent applications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual reference (e.g., publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Other embodiments are within the following claims.

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<220> FEATURE:
<223> OTHER INFORMATION: adeno-associated virus 9

<400> SEQUENCE: 1

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
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        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 2
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate
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<400> SEQUENCE: 2

Met Thr Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Gln Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415
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Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 3
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 3

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45
```

```
Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460
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```
Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Gly Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Gly Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 4
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 4

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Ile Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95
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```
Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
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        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Tyr Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 5
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 5

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1           5                       10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Asp
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                              -continued
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575
```

```
Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735
```

<210> SEQ ID NO 6
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 6

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Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Leu Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205
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Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Ser Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620
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Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 7
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 7

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255
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Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Arg Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
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        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 8
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 8

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Val Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
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305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735
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<210> SEQ ID NO 9
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 9

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Arg Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365
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Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 10
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 10
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Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Cys Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415
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```
Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 11
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 11

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45
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```
Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Arg Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
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465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Lys Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 12
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 12

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
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            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro His Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Asn
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Arg Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525
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Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Met Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 13
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 13

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160
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Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Arg Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575
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Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 14
<211> LENGTH: 145
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 14

ttggccactc cctctctgcg cgctcgctcg ctcactgagg ccgggcgacc aaaggtcgcc     60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag agagggagtg    120

gccaactcca tcactagggg ttcct                                          145


<210> SEQ ID NO 15
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 15

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125
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Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Arg Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540
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Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Arg Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 16
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 16

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175
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Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Ala Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Arg Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
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        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 17
<211> LENGTH: 736
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV isolate

<400> SEQUENCE: 17

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1               5                   10                  15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
            20                  25                  30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
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225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335

Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Ile Ala Trp Pro Arg Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
                565                 570                 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
            580                 585                 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655
```

```
Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
    690                 695                 700

Tyr Cys Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735


<210> SEQ ID NO 18
<211> LENGTH: 145
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 18

aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg ctcactgagg      60

ccgggcgacc aaaggtcgcc cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc     120

gagcgcgcag agagggagtg gccaa                                           145


<210> SEQ ID NO 19
<211> LENGTH: 106
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 19

ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgaccttt      60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtgg                    106


<210> SEQ ID NO 20
<211> LENGTH: 167
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 20

ctctcccccc tgtcgcgttc gctcgctcgc tggctcgttt ggggggggtgg cagctcaaag      60

agctgccaga cgacggccct ctggccgtcg cccccccaaa cgagccagcg agcgagcgaa     120

cgcgacaggg gggagagtgc cacactctca agcaaggggg ttttgta                   167


<210> SEQ ID NO 21
<211> LENGTH: 167
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 21

tacaaaacct ccttgcttga gagtgtggca ctctcccccc tgtcgcgttc gctcgctcgc      60

tggctcgttt gggggggtgg cagctcaaag agctgccaga cgacggccct ctggccgtcg     120

cccccccaaa cgagccagcg agcgagcgaa cgcgacaggg gggagag                   167
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<210> SEQ ID NO 22
<211> LENGTH: 621
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: AAV2 Rep

<400> SEQUENCE: 22

Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp
1               5                   10                  15

Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Asn Trp Val Ala Glu
            20                  25                  30

Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
        35                  40                  45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
    50                  55                  60

Thr Glu Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
65                  70                  75                  80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Met His Val Leu Val Glu
                85                  90                  95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
            100                 105                 110

Arg Glu Lys Leu Ile Gln Arg Ile Tyr Arg Gly Ile Glu Pro Thr Leu
        115                 120                 125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
    130                 135                 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
145                 150                 155                 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Gln Tyr Leu
                165                 170                 175

Ser Ala Cys Leu Asn Leu Thr Glu Arg Lys Arg Leu Val Ala Gln His
            180                 185                 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Gln Asn
        195                 200                 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
    210                 215                 220

Met Glu Leu Val Gly Trp Leu Val Asp Lys Gly Ile Thr Ser Glu Lys
225                 230                 235                 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
                245                 250                 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
            260                 265                 270

Ile Met Ser Leu Thr Lys Thr Ala Pro Asp Tyr Leu Val Gly Gln Gln
        275                 280                 285

Pro Val Glu Asp Ile Ser Ser Asn Arg Ile Tyr Lys Ile Leu Glu Leu
    290                 295                 300

Asn Gly Tyr Asp Pro Gln Tyr Ala Ala Ser Val Phe Leu Gly Trp Ala
305                 310                 315                 320

Thr Lys Lys Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
                325                 330                 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Thr Val Pro
            340                 345                 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
        355                 360                 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
```

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    370                 375                 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
385                 390                 395                 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
                405                 410                 415

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
            420                 425                 430

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
        435                 440                 445

Glu Leu Thr Arg Arg Leu Asp His Asp Phe Gly Lys Val Thr Lys Gln
    450                 455                 460

Glu Val Lys Asp Phe Phe Arg Trp Ala Lys Asp His Val Val Glu Val
465                 470                 475                 480

Glu His Glu Phe Tyr Val Lys Lys Gly Gly Ala Lys Lys Arg Pro Ala
                485                 490                 495

Pro Ser Asp Ala Asp Ile Ser Glu Pro Lys Arg Val Arg Glu Ser Val
            500                 505                 510

Ala Gln Pro Ser Thr Ser Asp Ala Glu Ala Ser Ile Asn Tyr Ala Asp
        515                 520                 525

Arg Tyr Gln Asn Lys Cys Ser Arg His Val Gly Met Asn Leu Met Leu
    530                 535                 540

Phe Pro Cys Arg Gln Cys Glu Arg Met Asn Gln Asn Ser Asn Ile Cys
545                 550                 555                 560

Phe Thr His Gly Gln Lys Asp Cys Leu Glu Cys Phe Pro Val Ser Glu
                565                 570                 575

Ser Gln Pro Val Ser Val Val Lys Lys Ala Tyr Gln Lys Leu Cys Tyr
            580                 585                 590

Ile His His Ile Met Gly Lys Val Pro Asp Ala Cys Thr Ala Cys Asp
        595                 600                 605

Leu Val Asn Val Asp Leu Asp Asp Cys Ile Phe Glu Gln
    610                 615                 620


<210> SEQ ID NO 23
<211> LENGTH: 960
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 23

gcttcaggag cagttgtgcg aatagctgga gaacaccagg ctggatttaa acccagatcg      60

ctcttacatt tgctctttac ctgctgtgct cagcgttcac gtgccctcta gctgtagttt     120

tctgaagtca gcgcacagca aggcagtgtg cttagaggtt aacagaaggg aaaacaacaa     180

caacaaaaat ctaaatgaga atcctgactg tttcagctgg gggtaagggg ggcggattat     240

tcatataatt gttataccag acggtcgcag gcttagtcca attgcagaga actcgcttcc     300

caggcttctg agagtcccgg aagtgcctaa acctgtctaa tcgacggggc ttgggtggcc     360

cgtcgctccc tggcttcttc cctttaccca gggcgggcag cgaagtggtg cctcctgcgt     420

cccccacacc ctccctcagc ccctcccctc cggcccgtcc tgggcaggtg acctggagca     480

tccggcaggc tgccctggcc tcctgcgtca ggacaacgcc cacgaggggc gttactgtgc     540

ggagatgcac cacgcaagag acaccctttg taactctctt ctcctcccta gtgcgaggtt     600

aaaaccttca gccccacgtg ctgtttgcaa acctgcctgt acctgaggcc ctaaaaagcc     660
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agagacctca ctcccgggga gccagcatgt ccactgcggt cctggaaaac ccaggcttgg 720

gcaggaaact ctctgacttt ggacaggtga gccacggcag cctgagctgc tcagttaggg 780

gaatttgggc ctccagagaa agagatctga agactgctgg tgcttcctgg tttcataagc 840

tcagtaagaa gtctgaattc gttggaagct gatgagaata tccaggaagt caacagacaa 900

atgtcctcaa caattgtttc taagtaggag aacatctgtc ctcggtggct ttcacaggaa 960

<210> SEQ ID NO 24
<211> LENGTH: 910
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 24

ctgggatggg atgtggaatc cttctagatt tcttttgtaa tatttataaa gtgctctcag 60

caaggtatca aaatggcaaa attgtgagta actatcctcc tttcattttg ggaagaagat 120

gaggcatgaa gagaattcag acagaaactt actcagacca ggggaggcag aaactaagca 180

gagaggaaaa tgaccaagag ttagccctgg gcatggaatg tgaaagaacc ctaaacgtga 240

cttggaaata atgcccaagg tatattccat tctccgggat ttgttggcat tttcttgagg 300

tgaagaattg cagaatacat tctttaatgt gacctacata tttacccatg ggaggaagtc 360

tgctcctgga ctcttgagat tcagtcataa agcccaggcc agggaaataa tgtaagtctg 420

caggcccctg tcatcagtag gattagggag aagagttctc agtagaaaac agggaggctg 480

gagagaaaag aatggttaat gttaacgtta atataactag aaagactgca gaacttagga 540

ctgattttta tttgaatcct taaaaaaaaa atttcttatg aaaatagtac atggctctta 600

ggagacagaa cttattgtac agaggaacag cgtgagagtc agagtgatcc cagaacaggt 660

cctggctcca tcctgcacat agttttggtg ctgctggcaa tacggtcccc acaactgtgg 720

gaaggggtta ggggcaggga tctcatcagg aaagcatagg ggtttaaagt tctttataga 780

gcacttagaa gattgagaat ccacaaatta tattaataac aaacaaagta gtgtcgtgtt 840

atatagtaaa tgtgaatttg cagacacatt tagggaaaag ttataattaa aaaaataggc 900

tgtatatata 910

<210> SEQ ID NO 25
<211> LENGTH: 192
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 25

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 60

tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 120

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 180

agtgtgagag gg 192

<210> SEQ ID NO 26
<211> LENGTH: 255
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 26

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aatgactcct ttcggtaagt gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc 60

agcgtaggcg ggcgactcag atcccagcca gtggacttag cccctgtttg ctcctccgat 120

aactggggtg accttggtta atattcacca gcagcctccc ccgttgcccc tctggatcca 180

ctgcttaaat acggacgagg acagggccct gtctcctcag cttcaggcac caccactgac 240

ctgggacagt gaatc 255

<210> SEQ ID NO 27
<211> LENGTH: 448
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 27

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 60

tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 120

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 180

agtgtgagag gggaatgact cctttcggta agtgcagtgg aagctgtaca ctgcccaggc 240

aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact tagcccctgt 300

ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct cccccgttgc 360

ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct cagcttcagg 420

caccaccact gacctgggac agtgaatc 448

<210> SEQ ID NO 28
<211> LENGTH: 1356
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 28

atgtccaccg ctgtgctgga gaaccctggg ctggggagga aactgtcaga cttcgggcag 60

gagacttcat acattgagga taactgtaac cagaatggcg ccatctctct gatcttcagc 120

ctgaaggagg aagtgggcgc cctggcaaag gtgctgcgcc tgtttgagga gaacgacgtg 180

aatctgaccc acatcgagtc ccggccttct agactgaaga aggacgagta cgagttcttt 240

acccacctgg ataagcggtc cctgccagcc ctgacaaaca tcatcaagat cctgaggcac 300

gacatcggag caaccgtgca cgagctgtct cgggacaaga agaaggatac cgtgccctgg 360

ttccctcgga caatccagga gctggataga tttgccaacc agatcctgtc ttacggagca 420

gagctggacg cagatcaccc tggcttcaag gacccagtgt atcgggcccg gagaaagcag 480

tttgccgata tcgcctacaa ttataggcac ggacagccaa tccctcgcgt ggagtatatg 540

gaggaggaga agaagacctg ggcacagtg ttcaagaccc tgaagagcct gtacaagaca 600

cacgcctgct acgagtataa ccacatcttc cccctgctgg agaagtattg tggctttcac 660

gaggacaata tccctcagct ggaggacgtg agccagttcc tgcagacctg cacaggcttt 720

aggctgaggc cagtggcagg actgctgagc tcccgggact tcctgggagg actggccttc 780

agagtgtttc actgcaccca gtacatcagg cacggctcca agccaatgta tacaccagag 840

cccgacatct gtcacgagct gctgggccac gtgcccctgt ttagcgatag atccttcgcc 900

cagttttccc aggagatcgg actggcatct ctgggagcac ctgacgagta catcgagaag 960 ctggccacca tctattggtt cacagtggag tttggcctgt gcaagcaggg cgatagcatc 1020

aaggcctacg gagcaggact gctgtctagc ttcggcgagc tgcagtattg tctgtccgag 1080

aagccaaagc tgctgcccct ggagctggag aagaccgcca tccagaacta caccgtgaca 1140

gagttccagc ccctgtacta tgtggccgag tcttttaacg atgccaagga gaaggtgaga 1200

aatttcgccg ccacaatccc taggcccttc agtgtgcgtt acgaccctta tacccagagg 1260

atcgaggtgc tggataatac acagcagctg aagatcctgg ctgactcaat caatagcgaa 1320

atcggaatcc tgtgctccgc cctgcagaaa atcaaa 1356

<210> SEQ ID NO 29
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 29

ctctaaggta aatataaaat ttttaagtgt ataatgtgtt aaactactga ttctaattgt 60

ttctctcttt tagattccaa cctttggaac tga 93

<210> SEQ ID NO 30
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 30

ctgacctctt ctcttcctcc cacagg 26

<210> SEQ ID NO 31
<211> LENGTH: 198
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 31

gatccagaca tgataagata cattgatgag tttggacaaa ccacaactag aatgcagtga 60

aaaaaatgct ttatttgtga aatttgtgat gctattgctt tatttgtaac cattataagc 120

tgcaataaac aagttaacaa caacaattgc attcatttta tgtttcaggt tcagggggag 180

gtgtgggagg ttttttaa 198

<210> SEQ ID NO 32
<211> LENGTH: 143
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 32

aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg ctcactgagg 60

ccgggcgacc aaaggtcgcc cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc 120

gagcgcgcag agagggagtg gcc 143

<210> SEQ ID NO 33
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 33

Met Ser Thr Ala Val Leu Glu Asn Pro Gly Leu Gly Arg Lys Leu Ser
1               5                   10                  15

Asp Phe Gly Gln Glu Thr Ser Tyr Ile Glu Asp Asn Cys Asn Gln Asn
            20                  25                  30

Gly Ala Ile Ser Leu Ile Phe Ser Leu Lys Glu Glu Val Gly Ala Leu
        35                  40                  45

Ala Lys Val Leu Arg Leu Phe Glu Glu Asn Asp Val Asn Leu Thr His
    50                  55                  60

Ile Glu Ser Arg Pro Ser Arg Leu Lys Lys Asp Glu Tyr Glu Phe Phe
65                  70                  75                  80

Thr His Leu Asp Lys Arg Ser Leu Pro Ala Leu Thr Asn Ile Ile Lys
                85                  90                  95

Ile Leu Arg His Asp Ile Gly Ala Thr Val His Glu Leu Ser Arg Asp
            100                 105                 110

Lys Lys Lys Asp Thr Val Pro Trp Phe Pro Arg Thr Ile Gln Glu Leu
        115                 120                 125

Asp Arg Phe Ala Asn Gln Ile Leu Ser Tyr Gly Ala Glu Leu Asp Ala
    130                 135                 140

Asp His Pro Gly Phe Lys Asp Pro Val Tyr Arg Ala Arg Arg Lys Gln
145                 150                 155                 160

Phe Ala Asp Ile Ala Tyr Asn Tyr Arg His Gly Gln Pro Ile Pro Arg
                165                 170                 175

Val Glu Tyr Met Glu Glu Glu Lys Lys Thr Trp Gly Thr Val Phe Lys
            180                 185                 190

Thr Leu Lys Ser Leu Tyr Lys Thr His Ala Cys Tyr Glu Tyr Asn His
        195                 200                 205

Ile Phe Pro Leu Leu Glu Lys Tyr Cys Gly Phe His Glu Asp Asn Ile
    210                 215                 220

Pro Gln Leu Glu Asp Val Ser Gln Phe Leu Gln Thr Cys Thr Gly Phe
225                 230                 235                 240

Arg Leu Arg Pro Val Ala Gly Leu Leu Ser Ser Arg Asp Phe Leu Gly
                245                 250                 255

Gly Leu Ala Phe Arg Val Phe His Cys Thr Gln Tyr Ile Arg His Gly
            260                 265                 270

Ser Lys Pro Met Tyr Thr Pro Glu Pro Asp Ile Cys His Glu Leu Leu
        275                 280                 285

Gly His Val Pro Leu Phe Ser Asp Arg Ser Phe Ala Gln Phe Ser Gln
    290                 295                 300

Glu Ile Gly Leu Ala Ser Leu Gly Ala Pro Asp Glu Tyr Ile Glu Lys
305                 310                 315                 320

Leu Ala Thr Ile Tyr Trp Phe Thr Val Glu Phe Gly Leu Cys Lys Gln
                325                 330                 335

Gly Asp Ser Ile Lys Ala Tyr Gly Ala Gly Leu Leu Ser Ser Phe Gly
            340                 345                 350

Glu Leu Gln Tyr Cys Leu Ser Glu Lys Pro Lys Leu Leu Pro Leu Glu
        355                 360                 365

Leu Glu Lys Thr Ala Ile Gln Asn Tyr Thr Val Thr Glu Phe Gln Pro
    370                 375                 380

Leu Tyr Tyr Val Ala Glu Ser Phe Asn Asp Ala Lys Glu Lys Val Arg
385                 390                 395                 400

Asn Phe Ala Ala Thr Ile Pro Arg Pro Phe Ser Val Arg Tyr Asp Pro
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                405                 410                 415

Tyr Thr Gln Arg Ile Glu Val Leu Asp Asn Thr Gln Gln Leu Lys Ile
            420                 425                 430

Leu Ala Asp Ser Ile Asn Ser Glu Ile Gly Ile Leu Cys Ser Ala Leu
        435                 440                 445

Gln Lys Ile Lys
    450


<210> SEQ ID NO 34
<211> LENGTH: 122
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 34

aacttgttta ttgcagctta taatggttac aaataaagca atagcatcac aaatttcaca      60

aataaagcat ttttttcact gcattctagt tgtggtttgt ccaaactcat caatgtatct     120

ta                                                                    122


<210> SEQ ID NO 35
<211> LENGTH: 133
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 35

tgctttattt gtgaaatttg tgatgctatt gctttatttg taaccattat aagctgcaat      60

aaacaagtta acaacaacaa ttgcattcat tttatgtttc aggttcaggg ggaggtgtgg     120

gaggtttttt aaa                                                        133


<210> SEQ ID NO 36
<211> LENGTH: 1676
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 36

ggcattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc      60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca     120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga     180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc     240

aagtgtatca tatgccaagt ccgcccccta ttgacgtcaa tgacggtaaa tggcccgcct     300

ggcattatgc ccagtacatg accttacggg actttcctac ttggcagtac atctacgtat     360

tagtcatcgc tattaccatg gtcgaggtga gccccacgtt ctgcttcact ctccccatct     420

cccccccctc cccaccccca attttgtatt tatttatttt ttaattattt tgtgcagcga     480

tgggggcggg gggggggggg gggcgcgcgc caggcggggc ggggcggggc gaggggcggg     540

gcggggcgag gcggagaggt gcggcggcag ccaatcagag cggcgcgctc cgaaagtttc     600

cttttatggc gaggcggcgg cggcggcggc cctataaaaa gcgaagcgcg cggcgggcgg     660

gagtcgctgc gcgctgcctt cgccccgtgc cccgctccgc cgccgcctcg cgccgcccgc     720

cccggctctg actgaccgcg ttactcccac aggtgagcgg gcgggacggc ccttctcctc     780
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cgggctgtaa ttagcgcttg gtttaatgac ggcttgtttc ttttctgtgg ctgcgtgaaa 840

gccttgaggg gctccgggag ggccctttgt gcggggggag cggctcgggg ggtgcgtgcg 900

tgtgtgtgtg cgtggggagc gccgcgtgcg gctccgcgct gcccggcggc tgtgagcgct 960

gcgggcgcgg cgcggggctt tgtgcgctcc gcagtgtgcg cgaggggagc gcggccgggg 1020

gcggtgcccc gcggtgcggg gggggctgcg aggggaacaa aggctgcgtg cggggtgtgt 1080

gcgtgggggg gtgagcaggg ggtgtgggcg cgtcggtcgg gctgcaaccc cccctgcacc 1140

cccctccccg agttgctgag cacggcccgg cttcgggtgc ggggctccgt acggggcgtg 1200

gcgcggggct cgccgtgccg ggcggggggt ggcggcaggt gggggtgccg ggcggggcgg 1260

ggccgcctcg ggccggggag ggctcggggg aggggcgcgg cggcccccgg agcgccggcg 1320

gctgtcgagg cgcggcgagc cgcagccatt gccttttatg gtaatcgtgc gagagggcgc 1380

agggacttcc tttgtcccaa atctgtgcgg agccgaaatc tgggaggcgc cgccgcaccc 1440

cctctagcgg gcgcggggcg aagcggtgcg gcgccggcag gaaggaaatg ggcggggagg 1500

gccttcgtgc gtcgccgcgc cgccgtcccc ttctccctct ccagcctcgg ggctgtccgc 1560

gggggacgg ctgccttcgg gggggacggg gcagggcggg gttcggcttc tggcgtgtga 1620

ccggcggctc tagagcctct gctaaccatg ttcatgcctt cttcttttc ctacag 1676

<210> SEQ ID NO 37
<211> LENGTH: 960
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 37

gcttcaggag cagttgtgcg aatagctgga gaacaccagg ctggatttaa acccagatcg 60

ctcttacatt tgctctttac ctgctgtgct cagcgttcac gtgccctcta gctgtagttt 120

tctgaagtca gcgcacagca aggcagtgtg cttagaggtt aacagaaggg aaaacaacaa 180

caacaaaaat ctaaatgaga atcctgactg tttcagctgg gggtaagggg ggcggattat 240

tcatataatt gttataccag acggtcgcag gcttagtcca attgcagaga actcgcttcc 300

caggcttctg agagtcccgg aagtgcctaa acctgtctaa tcgacggggc ttgggtggcc 360

cgtcgctccc tggcttcttc cctttaccca gggcgggcag cgaagtggtg cctcctgcgt 420

cccccacacc ctccctcagc ccctcccctc cggcccgtcc tgggcaggtg acctggagca 480

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gcaggaaact ctctgacttt ggacaggtga gccacggcag cctgagctgc tcagttaggg 780

gaatttgggc ctccagagaa agagatccga agactgctgg tgcttcctgg tttcataagc 840

tcagtaagaa gtctgaattc gttggaagct gatgagaata tccaggaagt caacagacaa 900

atgtcctcaa caattgtttc taagtaggag aacatctgtc ctcggtggct ttcacaggaa 960

<210> SEQ ID NO 38
<211> LENGTH: 911
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 38

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caaggtatca aaatggcaaa attgtgagta actatcctcc tttcattttg ggaagaagat 120

gaggcatgaa gagaattcag acagaaactt actcagacca ggggaggcag aaactaagca 180

gagaggaaaa tgaccaagag ttagccctgg gcatggaatg tgaaagaacc ctaaacgtga 240

cttggaaata atgcccaagg tatattccat tctccgggat ttgttggcat tttcttgagg 300

tgaagaattg cagaatacat tctttaatgt gacctacata tttacccatg ggaggaagtc 360

tgctcctgga ctcttgagat tcagtcataa agcccaggcc agggaaataa tgtaagtctg 420

caggcccctg tcatcagtag gattagggag aagagttctc agtagaaaac agggaggctg 480

gagagaaaag aatggttaat gttaacgtta atataactag aaagactgca gaacttagga 540

ctgattttta tttgaatcct taaaaaaaaa aatttcttat gaaaatagta catggctctt 600

aggagacaga acttattgta cagaggaaca gcgtgagagt cagagtgatc ccagaacagg 660

tcctggctcc atcctgcaca tagttttggt gctgctggca atacggtccc cacaactgtg 720

ggaaggggtt aggggcaggg atctcatcag gaaagcatag ggtttaaag ttctttatag 780

agcacttaga agattgagaa tccacaaatt atattaataa caaacaaagt agtgtcgtgt 840

tatatagtaa atgtgaattt gcagacacat ttagggaaaa gttataatta aaaaaatagg 900

ctgtatatat a 911

<210> SEQ ID NO 39
<211> LENGTH: 1168
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 39

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tggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 120

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 180

gtgcagtagt cgccgtgaac gttctttttc gcaacgggtt tgccgccaga acacaggtaa 240

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gccttgcgct ttaggagccc cttcgcctcg tgcttgagtt gaggcctggc ctgggcgctg 420

gggccgccgc gtgcgaatct ggtggcacct tcgcgcctgt ctcgctgctt tcgataagtc 480

tctagccatt taaaattttt gatgacctgc tgcgacgctt tttttctggc aagatagtct 540

tgtaaatgcg ggccaggatc tgcacactgg tatttcggtt tttggggccg cgggcggcga 600

cggggcccgt gcgtcccagc gcacatgttc ggcgaggcgg ggcctgcgag cgcggccacc 660

gagaatcgga cgggggtagt ctcaagctgg ccggcctgct ctggtgcctg gcctcgcgcc 720

gccgtgtatc gccccgccct gggcggcaag gctggcccgg tcggcaccag ttgcgtgagc 780

ggaaagatgg ccgcttcccg gccctgctcc agggggctca aaatggagga cgcggcgctc 840

gggagagcgg gcgggtgagt cacccacaca aaggaaaggg gcctttccgt cctcagccgt 900

cgcttcatgt gactccacgg agtaccgggc gccgtccagg cacctcgatt agttctggag 960

cttttggagt acgtcgtctt taggttgggg ggaggggttt tatgcgatgg agtttcccca 1020

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cactgagtgg gtggagactg aagttaggcc agcttggcac ttgatgtaat tctccttgga 1080

atttgccctt tttgagtttg gatcttggtt cattctcaag cctcagacag tggttcaaag 1140

tttttttctt ccatttcagg tgtcgtga 1168

<210> SEQ ID NO 40
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 40

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cccggcccta gg 72

<210> SEQ ID NO 41
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 41

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ttattgtgct gtctcatcat tttggcaaag aattc 95

<210> SEQ ID NO 42
<211> LENGTH: 1873
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 42

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ggctattggc cattgcatac gttgtatcta tatcataata tgtacattta tattggctca 120

tgtccaatat gaccgccatg ttggcattga ttattgacta gttattaata gtaatcaatt 180

acggggtcat tagttcatag cccatatatg gagttccgcg ttacataact tacggtaaat 240

ggcccgcctg gctgaccgcc caacgacccc cgcccattga cgtcaataat gacgtatgtt 300

cccatagtaa cgccaatagg gactttccat tgacgtcaat gggtggagta tttacggtaa 360

actgcccact tggcagtaca tcaagtgtat catatgccaa gtccgccccc tattgacgtc 420

aatgacggta aatggcccgc ctggcattat gcccagtaca tgaccttacg ggactttcct 480

acttggcagt acatctacgt attagtcatc gctattacca tggtcgaggt gagccccacg 540

ttctgcttca ctctccccat ctcccccccc tccccacccc caattttgta tttatttatt 600

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ttcttttctg tggctgcgtg aaagccttga ggggctccgg gagggccctt tgtgcggggg 1020

ggagcggctc gggggtgcg tgcgtgtgtg tgtgcgtggg gagcgccgcg tgcggcccgc 1080

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gctgcccggc ggctgtgagc gctgcgggcg cggcgcgggg ctttgtgcgc tccgcagtgt 1140

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cgggctgtaa cccccccctg caccccccctc cccgagttgc tgagcacggc ccggcttcgg 1320

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tatggtaatc gtgcgagagg gcgcagggac ttcctttgtc ccaaatctgt gcggagccga 1560

aatctgggag gcgccgccgc acccccctcta gcgggcgcgg ggcgaagcgg tgcggcgccg 1620

gcaggaagga aatgggcggg gagggccttc gtgcgtcgcc gcgccgccgt ccccttctcc 1680

ctctccagcc tcggggctgt ccgcgggggg acggctgcct tcgggggga cggggcaggg 1740

cggggttcgg cttctggcgt gtgaccggcg gctctagagc ctctgctaac catgttcatg 1800

ccttcttctt tttcctacag ctcctgggca acgtgctggt tattgtgctg tctcatcatt 1860

ttggcaaaga att 1873

<210> SEQ ID NO 43
<211> LENGTH: 4046
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 43

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ctcttacatt tgctctttac ctgctgtgct cagcgttcac gtgccctcta gctgtagttt 120

tctgaagtca gcgcacagca aggcagtgtg cttagaggtt aacagaaggg aaaacaacaa 180

caacaaaaat ctaaatgaga atcctgactg tttcagctgg gggtaagggg ggcggattat 240

tcatataatt gttataccag acggtcgcag gcttagtcca attgcagaga actcgcttcc 300

caggcttctg agagtcccgg aagtgcctaa acctgtctaa tcgacggggc ttgggtggcc 360

cgtcgctccc tggcttcttc cctttaccca gggcgggcag cgaagtggtg cctcctgcgt 420

cccccacacc ctccctcagc ccctcccctc cggcccgtcc tgggcaggtg acctggagca 480

tccggcaggc tgccctggcc tcctgcgtca ggacaacgcc cacgaggggc gttactgtgc 540

ggagatgcac cacgcaagag acaccctttg taactctctt ctcctcccta gtgcgaggtt 600

aaaaccttca gccccacgtg ctgtttgcaa acctgcctgt acctgaggcc ctaaaaagcc 660

agagacctca ctcccgggga gccagcatgt ccactgcggt cctggaaaac ccaggcttgg 720

gcaggaaact ctctgacttt ggacaggtga gccacggcag cctgagctgc tcagttaggg 780

gaatttgggc ctccagagaa agagatctga agactgctgg tgcttcctgg tttcataagc 840

tcagtaagaa gtctgaattc gttggaagct gatgagaata tccaggaagt caacagacaa 900

atgtcctcaa caattgtttc taagtaggag aacatctgtc ctcggtggct ttcacaggaa 960

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 1020

tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 1080

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 1140

agtgtgagag gggaatgact cctttcggta agtgcagtgg aagctgtaca ctgcccaggc 1200

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aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact tagcccctgt   1260

ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct cccccgttgc   1320

ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct cagcttcagg   1380

caccaccact gacctgggac agtgaatcct ctaaggtaaa tataaaattt ttaagtgtat   1440

aatgtgttaa actactgatt ctaattgttt ctctctttta gattccaacc tttggaactg   1500

accgccacca tgtccaccgc tgtgctggag aaccctgggc tggggaggaa actgtcagac   1560

ttcgggcagg agacttcata cattgaggat aactgtaacc agaatggcgc catctctctg   1620

atcttcagcc tgaaggagga agtgggcgcc ctggcaaagg tgctgcgcct gtttgaggag   1680

aacgacgtga atctgaccca catcgagtcc cggccttcta gactgaagaa ggacgagtac   1740

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ctgaggcacg acatcggagc aaccgtgcac gagctgtctc gggacaagaa gaaggatacc   1860

gtgccctggt tccctcggac aatccaggag ctggatagat ttgccaacca gatcctgtct   1920

tacggagcag agctggacgc agatcaccct ggcttcaagg acccagtgta tcgggcccgg   1980

agaaagcagt ttgccgatat cgcctacaat tataggcacg gacagccaat ccctcgcgtg   2040

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tctcgagcct ctagaactat agtgagtcgt attacgtaga tccagacatg ataagataca   2940

ttgatgagtt tggacaaacc acaactagaa tgcagtgaaa aaaatgcttt atttgtgaaa   3000

tttgtgatgc tattgcttta tttgtaacca ttataagctg caataaacaa gttaacaaca   3060

acaattgcat tcattttatg tttcaggttc agggggaggt gtgggaggtt ttttaagctt   3120

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cccatgggag gaagtctgct cctggactct tgagattcag tcataaagcc caggccaggg   3540

aaataatgta agtctgcagg cccctgtcat cagtaggatt agggagaaga gttctcagta   3600
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gaaaacaggg aggctggaga gaaaagaatg gttaatgtta acgttaatat aactagaaag 3660

actgcagaac ttaggactga tttttatttg aatccttaaa aaaaaaattt cttatgaaaa 3720

tagtacatgg ctcttaggag acagaactta ttgtacagag gaacagcgtg agagtcagag 3780

tgatcccaga acaggtcctg gctccatcct gcacatagtt ttggtgctgc tggcaatacg 3840

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taaagttctt tatagagcac ttagaagatt gagaatccac aaattatatt aataacaaac 3960

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aattaaaaaa ataggctgta tatata 4046

<210> SEQ ID NO 44
<211> LENGTH: 913
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 44

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cgaagaggac caatttcttc caggaggaca actacctcgt cctctgcaga cccctctcct 180

cggcagctga aggagtgtgg ccaatctgcc tccacctccc cgcggacccc ctactctcag 240

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cgggagccgg cagccctagt ggagcggttg gagatgttga ggtgggaggg tcacccaggt 360

ggggtgaggc tggggtaggt agcggagtga acggcttccg aagctctggg ccgcccccag 420

gttggactaa gcaggcgctc tgtcttcgcc cccgcccagg gtgggcgtct cctgaggact 480

ccccgccaca cctgacccga gaccgcgcgc ccagcctaga acgcttcccc gacccagcgt 540

agggccgccg cgactggcgg gcgagggtcg gcgggaggcc tggcgaaccc gggggcggga 600

ccaggcgggc aaggcccggc tgccgcagcg ccgctctgcg cgaggcggct ccgccgcggc 660

ggagggatac ggcgcaccat atatatatcg cggggcgcag actcgcgctc cggcagtggt 720

gctgggagtg tcgtggacgc cgtgccgtta ctcgtagtca ggcggcggcg caggcggcgg 780

cggcggcata gcgcacagcg cgccttagca gcagcagcag cagcagcggc atcggaggta 840

cccccgccgt cgcagccccc gcgctggtgc agccaccctc gctccctctg ctcttcctcc 900

cttcgctcgc acc 913

<210> SEQ ID NO 45
<211> LENGTH: 4452
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 45

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gccaactcca tcactagggg ttcctggagg ggtggagtcg tgacgtgaat tacgtcatag 180

ggttagggag gtcctgcata tgcggccgct tcaggagcag ttgtgcgaat agctggagaa 240

caccaggctg gatttaaacc cagatcgctc ttacatttgc tctttacctg ctgtgctcag 300

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cgttcacgtg ccctctagct gtagttttct gaagtcagcg cacagcaagg cagtgtgctt    360

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cagctggggg taagggggc ggattattca tataattgtt ataccagacg gtcgcaggct    480

tagtccaatt gcagagaact cgcttcccag gcttctgaga gtcccggaag tgcctaaacc    540

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ctctcttctc ctccctagtg cgaggttaaa accttcagcc ccacgtgctg tttgcaaacc    840

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ctgcggtcct ggaaaaccca ggcttgggca ggaaactctc tgactttgga caggtgagcc    960

acggcagcct gagctgctca gttaggggaa tttgggcctc cagagaaaga gatctgaaga   1020

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ctctgggccc atgccacctc caacatccac tcgacccctt ggaatttcgg tggagaggag   1320

cagaggttgt cctggcgtgg tttaggtagt gtgagagggg aatgactcct ttcggtaagt   1380

gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc agcgtaggcg ggcgactcag   1440

atcccagcca gtggacttag cccctgtttg ctcctccgat aactggggtg accttggtta   1500

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acagggccct gtctcctcag cttcaggcac caccactgac ctgggacagt gaatcctcta   1620

aggtaaatat aaaattttta agtgtataat gtgttaaact actgattcta attgtttctc   1680

tcttttagat tccaaccttt ggaactgacc gccaccatgt ccaccgctgt gctggagaac   1740

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gatagatttg ccaaccagat cctgtcttac ggagcagagc tggacgcaga tcaccctggc   2160

ttcaaggacc cagtgtatcg ggcccggaga aagcagtttg ccgatatcgc ctacaattat   2220

aggcacggac agccaatccc tcgcgtggag tatatggagg aggagaagaa gacctggggc   2280

acagtgttca agaccctgaa gagcctgtac aagacacacg cctgctacga gtataaccac   2340

atcttccccc tgctggagaa gtattgtggc tttcacgagg acaatatccc tcagctggag   2400

gacgtgagcc agttcctgca gacctgcaca ggctttaggc tgaggccagt ggcaggactg   2460

ctgagctccc gggacttcct gggaggactg gccttcagag tgtttcactg cacccagtac   2520

atcaggcacg gctccaagcc aatgtataca ccagagcccg acatctgtca cgagctgctg   2580

ggccacgtgc ccctgtttag cgatagatcc ttcgcccagt tttcccagga gatcggactg   2640

gcatctctgg gagcacctga cgagtacatc gagaagctgg ccaccatcta ttggttcaca   2700
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gtggagtttg gcctgtgcaa gcagggcgat agcatcaagg cctacggagc aggactgctg 2760

tctagcttcg gcgagctgca gtattgtctg tccgagaagc caaagctgct gcccctggag 2820

ctggagaaga ccgccatcca gaactacacc gtgacagagt tccagcccct gtactatgtg 2880

gccgagtctt ttaacgatgc caaggagaag gtgagaaatt tcgccgccac aatccctagg 2940

cccttcagtg tgcgttacga cccttatacc cagaggatcg aggtgctgga taatacacag 3000

cagctgaaga tcctggctga ctcaatcaat agcgaaatcg gaatcctgtg ctccgccctg 3060

cagaaaatca aatgagaatt caaggcctct cgagcctcta gaactatagt gagtcgtatt 3120

acgtagatcc agacatgata agatacattg atgagtttgg acaaaccaca actagaatgc 3180

agtgaaaaaa atgctttatt tgtgaaattt gtgatgctat tgctttattt gtaaccatta 3240

taagctgcaa taaacaagtt aacaacaaca attgcattca ttttatgttt caggttcagg 3300

gggaggtgtg ggaggttttt taagctttac gtacgatcgt cgactgggat gggatgtgga 3360

atccttctag atttcttttg taatatttat aaagtgctct cagcaaggta tcaaaatggc 3420

aaaattgtga gtaactatcc tcctttcatt ttgggaagaa gatgaggcat gaagagaatt 3480

cagacagaaa cttactcaga ccaggggagg cagaaactaa gcagagagga aaatgaccaa 3540

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gattcagtca taaagcccag gccagggaaa taatgtaagt ctgcaggccc ctgtcatcag 3780

taggattagg gagaagagtt ctcagtagaa aacagggagg ctggagagaa aagaatggtt 3840

aatgttaacg ttaatataac tagaaagact gcagaactta ggactgattt ttatttgaat 3900

ccttaaaaaa aaaatttctt atgaaaatag tacatggctc ttaggagaca gaacttattg 3960

tacagaggaa cagcgtgaga gtcagagtga tcccagaaca ggtcctggct ccatcctgca 4020

catagttttg gtgctgctgg caatacggtc cccacaactg tgggaagggg ttaggggcag 4080

ggatctcatc aggaaagcat aggggtttaa agttctttat agagcactta gaagattgag 4140

aatccacaaa ttatattaat aacaaacaaa gtagtgtcgt gttatatagt aaatgtgaat 4200

ttgcagacac atttagggaa aagttataat taaaaaaata ggctgtatat atacctgcag 4260

gtctagatac gtagataagt agcatggcgg gttaatcatt aactacaagg aacccctagt 4320

gatggagttg gccactccct ctctgcgcgc tcgctcgctc actgaggccg ggcgaccaaa 4380

ggtcgcccga cgcccgggct ttgcccgggc ggcctcagtg agcgagcgag cgcgcagaga 4440

gggagtggcc aa 4452

<210> SEQ ID NO 46
<211> LENGTH: 380
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 46

ggcattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240 aagtgtatca tatgccaagt ccgcccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttacggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg 380

<210> SEQ ID NO 47
<211> LENGTH: 1246
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 47

tcgaggtgag ccccacgttc tgcttcactc tccccatctc ccccccctcc ccacccccaa 60

ttttgtattt atttattttt taattatttt gtgcagcgat gggggcgggg gggggggggg 120

ggcgcgcgcc aggcggggcg gggcggggcg aggggcgggg cggggcgagg cggagaggtg 180

cggcggcagc caatcagagc ggcgcgctcc gaaagtttcc ttttatggcg aggcggcggc 240

ggcggcggcc ctataaaaag cgaagcgcgc ggcgggcggg agtcgctgcg cgctgccttc 300

gccccgtgcc ccgctccgcc gccgcctcgc gccgcccgcc ccggctctga ctgaccgcgt 360

tactcccaca ggtgagcggg cgggacggcc cttctcctcc gggctgtaat tagcgcttgg 420

tttaatgacg gcttgtttct tttctgtggc tgcgtgaaag ccttgagggg ctccgggagg 480

gccctttgtg cggggggagc ggctcggggg gtgcgtgcgt gtgtgtgtgc gtggggagcg 540

ccgcgtgcgg ctccgcgctg cccggcggct gtgagcgctg cgggcgcggc gcggggcttt 600

gtgcgctccg cagtgtgcgc gaggggagcg cggccggggg cggtgccccg cggtgcgggg 660

ggggctgcga ggggaacaaa ggctgcgtgc ggggtgtgtg cgtgggggggg tgagcagggg 720

gtgtgggcgc gtcggtcggg ctgcaacccc ccctgcaccc ccctccccga gttgctgagc 780

acggcccggc ttcgggtgcg gggctccgta cggggcgtgg cgcggggctc gccgtgccgg 840

gcgggggggtg gcggcaggtg gggggtgccgg gcggggcggg gccgcctcgg gccggggagg 900

gctcggggga ggggcgcggc ggcccccgga gcgccggcgg ctgtcgaggc gcggcgagcc 960

gcagccattg ccttttatgg taatcgtgcg agagggcgca gggacttcct ttgtcccaaa 1020

tctgtgcgga gccgaaatct gggaggcgcc gccgcacccc ctctagcggg cgcggggcga 1080

agcggtgcgg cgccggcagg aaggaaatgg gcggggaggg ccttcgtgcg tcgccgcgcc 1140

gccgtcccct tctccctctc cagcctcggg gctgtccgcg gggggacggc tgccttcggg 1200

ggggacgggg cagggcgggg ttcggcttct ggcgtgtgac cggcgg 1246

<210> SEQ ID NO 48
<211> LENGTH: 1061
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 48

tagggaggtc ctgcacgtta cataacttac ggtaaatggc ccgcctggct gaccgcccaa 60

cgacccccgc ccattgacgt caataatgac gtatgttccc atagtaacgc caatagggac 120

tttccattga cgtcaatggg tggagtattt acggtaaact gcccacttgg cagtacatca 180

agtgtatcat atgccaagta cgccccctat tgacgtcaat gacggtaaat ggcccgcctg 240

gcattatgcc cagtacatga ccttatggga ctttcctact tggcagtaca tctacgtatt 300

agtcatcgct attaccatgg tcgaggtgag ccccacgttc tgcttcactc tccccatctc 360 cccccccctcc ccacccccaa ttttgtattt atttattttt taattatttt gtgcagcgat 420

gggggcgggg gggggggggg gcgcgcgcca ggcggggcgg ggcggggcga ggggcggggc 480

ggggcgaggc ggagaggtgc ggcggcagcc aatcagagcg gcgcgctccg aaagtttcct 540

tttatggcga ggcggcggcg gcggcggccc tataaaaagc gaagcgcgcg gcgggcggga 600

gtcgctgcgc gctgccttcg ccccgtgccc cgctccgccg ccgcctcgcg ccgcccgccc 660

cggctctgac tgaccgcgtt actaaaacag gtaagtccgg cctccgcgcc gggttttggc 720

gcctcccgcg ggcgcccccc tcctcacggc gagcgctgcc acgtcagacg aagggcgcag 780

cgagcgtcct gatccttccg cccggacgct caggacagcg gcccgctgct cataagactc 840

ggccttagaa ccccagtatc agcagaagga cattttagga cgggacttgg gtgactctag 900

ggcactggtt ttctttccag agagcggaac aggcgaggaa aagtagtccc ttctcggcga 960

ttctgcggag ggatctccgt ggggcggtga acgccgatga tgcctctact aaccatgttc 1020

atgttttctt ttttttcta caggtcctgg gtgacgaaca g 1061

<210> SEQ ID NO 49
<211> LENGTH: 953
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 49

aattcggtac cctagttatt aatagtaatc aattacgggg tcattagttc atagcccata 60

tatggagttc cgcgttacat aacttacggt aaatggcccg cctggctgac cgcccaacga 120

cccccgccca ttgacgtcaa taatgacgta tgttcccata gtaacgccaa tagggacttt 180

ccattgacgt caatgggtgg actatttacg gtaaactgcc cacttggcag tacatcaagt 240

gtatcatatg ccaagtacgc cccctattga cgtcaatgac ggtaaatggc ccgcctggca 300

ttatgcccag tacatgacct tatgggactt tcctacttgg cagtacatct acgtattagt 360

catcgctatt accatggtcg aggtgagccc cacgttctgc ttcactctcc ccatctcccc 420

cccctcccca cccccaattt tgtatttatt tattttttaa ttattttgtg cagcgatggg 480

ggcggggggg gggggggggc gcgcgccagg cggggcgggg cggggcgagg ggcggggcgg 540

ggcgaggcgg agaggtgcgg cggcagccaa tcagagcggc gcgctccgaa agtttccttt 600

tatggcgagg cggcggcggc ggcggcccta taaaaagcga agcgcgcggc gggcgggagt 660

cgctgcgacg ctgccttcgc cccgtgcccc gctccgccgc cgcctcgcgc cgcccgcccc 720

ggctctgact gaccgcgtta ctcccacagg tgagcgggcg ggacggccct tctcctccgg 780

gctgtaatta gcgcttggtt taatgacggc ttgtttcttt tctgtggctg cgtgaaagcc 840

ttgaggggct ccgggagcta gagcctctgc taaccatgtt catgccttct tctttttcct 900

acagctcctg ggcaacgtgc tggttattgt gctgtctcat cattttggca aag 953

<210> SEQ ID NO 50
<211> LENGTH: 541
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 50

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 60 tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 120

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 180

agtgtgagag gggaatgact cctttcggta agtgcagtgg aagctgtaca ctgcccaggc 240

aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact tagcccctgt 300

ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct cccccgttgc 360

ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct cagcttcagg 420

caccaccact gacctgggac agtgaatcct ctaaggtaaa tataaaattt ttaagtgtat 480

aatgtgttaa actactgatt ctaattgttt ctctctttta gattccaacc tttggaactg 540

a 541

<210> SEQ ID NO 51
<211> LENGTH: 1908
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 51

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 60

tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 120

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 180

agtgtgagag gggaatgact cctttcggta agtgcagtgg aagctgtaca ctgcccaggc 240

aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact tagcccctgt 300

ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct cccccgttgc 360

ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct cagcttcagg 420

caccaccact gacctgggac agtgaatcct ctaaggtaaa tataaaattt ttaagtgtat 480

aatgtgttaa actactgatt ctaattgttt ctctctttta gattccaacc tttggaactg 540

accgccacca tgtccaccgc tgtgctggag aaccctgggc tggggaggaa actgtcagac 600

ttcgggcagg agacttcata cattgaggat aactgtaacc agaatggcgc catctctctg 660

atcttcagcc tgaaggagga agtgggcgcc ctggcaaagg tgctgcgcct gtttgaggag 720

aacgacgtga atctgaccca catcgagtcc cggccttcta gactgaagaa ggacgagtac 780

gagttcttta cccacctgga taagcggtcc ctgccagccc tgacaaacat catcaagatc 840

ctgaggcacg acatcggagc aaccgtgcac gagctgtctc gggacaagaa gaaggatacc 900

gtgccctggt tccctcggac aatccaggag ctggatagat ttgccaacca gatcctgtct 960

tacggagcag agctggacgc agatcaccct ggcttcaagg acccagtgta tcgggcccgg 1020

agaaagcagt ttgccgatat cgcctacaat tataggcacg gacagccaat ccctcgcgtg 1080

gagtatatgg aggaggagaa gaagacctgg ggcacagtgt tcaagaccct gaagagcctg 1140

tacaagacac acgcctgcta cgagtataac cacatcttcc ccctgctgga gaagtattgt 1200

ggctttcacg aggacaatat ccctcagctg gaggacgtga gccagttcct gcagacctgc 1260

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acaccagagc ccgacatctg tcacgagctg ctgggccacg tgcccctgtt tagcgataga 1440

tccttcgccc agttttccca ggagatcgga ctggcatctc tgggagcacc tgacgagtac 1500

atcgagaagc tggccaccat ctattggttc acagtggagt ttggcctgtg caagcagggc 1560

-continued

gatagcatca aggcctacgg agcaggactg ctgtctagct tcggcgagct gcagtattgt 1620

ctgtccgaga agccaaagct gctgcccctg gagctggaga agaccgccat ccagaactac 1680

accgtgacag agttccagcc cctgtactat gtggccgagt cttttaacga tgccaaggag 1740

aaggtgagaa atttcgccgc cacaatccct aggcccttca gtgtgcgtta cgacccttat 1800

acccagagga tcgaggtgct ggataataca cagcagctga agatcctggc tgactcaatc 1860

aatagcgaaa tcggaatcct gtgctccgcc ctgcagaaaa tcaaatga 1908

<210> SEQ ID NO 52
<211> LENGTH: 2156
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 52

ccctaaaatg ggcaaacatt gcaagcagca aacagcaaac acacagccct ccctgcctgc 60

tgaccttgga gctggggcag aggtcagaga cctctctggg cccatgccac ctccaacatc 120

cactcgaccc cttggaattt cggtggagag gagcagaggt tgtcctggcg tggtttaggt 180

agtgtgagag gggaatgact cctttcggta agtgcagtgg aagctgtaca ctgcccaggc 240

aaagcgtccg ggcagcgtag gcgggcgact cagatcccag ccagtggact tagcccctgt 300

ttgctcctcc gataactggg gtgaccttgg ttaatattca ccagcagcct cccccgttgc 360

ccctctggat ccactgctta aatacggacg aggacagggc cctgtctcct cagcttcagg 420

caccaccact gacctgggac agtgaatcct ctaaggtaaa tataaaattt ttaagtgtat 480

aatgtgttaa actactgatt ctaattgttt ctctctttta gattccaacc tttggaactg 540

accgccacca tgtccaccgc tgtgctggag aaccctgggc tggggaggaa actgtcagac 600

ttcgggcagg agacttcata cattgaggat aactgtaacc agaatggcgc catctctctg 660

atcttcagcc tgaaggagga agtgggcgcc ctggcaaagg tgctgcgcct gtttgaggag 720

aacgacgtga atctgaccca catcgagtcc cggccttcta gactgaagaa ggacgagtac 780

gagttcttta cccacctgga taagcggtcc ctgccagccc tgacaaacat catcaagatc 840

ctgaggcacg acatcggagc aaccgtgcac gagctgtctc gggacaagaa gaaggatacc 900

gtgccctggt tccctcggac aatccaggag ctggatagat ttgccaacca gatcctgtct 960

tacggagcag agctggacgc agatcaccct ggcttcaagg acccagtgta tcgggcccgg 1020

agaaagcagt ttgccgatat cgcctacaat tataggcacg gacagccaat ccctcgcgtg 1080

gagtatatgg aggaggagaa gaagacctgg ggcacagtgt tcaagaccct gaagagcctg 1140

tacaagacac acgcctgcta cgagtataac cacatcttcc ccctgctgga gaagtattgt 1200

ggctttcacg aggacaatat ccctcagctg gaggacgtga gccagttcct gcagacctgc 1260

acaggcttta ggctgaggcc agtggcagga ctgctgagct cccgggactt cctgggagga 1320

ctggccttca gagtgtttca ctgcacccag tacatcaggc acggctccaa gccaatgtat 1380

acaccagagc ccgacatctg tcacgagctg ctgggccacg tgcccctgtt tagcgataga 1440

tccttcgccc agttttccca ggagatcgga ctggcatctc tgggagcacc tgacgagtac 1500

atcgagaagc tggccaccat ctattggttc acagtggagt ttggcctgtg caagcagggc 1560

gatagcatca aggcctacgg agcaggactg ctgtctagct tcggcgagct gcagtattgt 1620

ctgtccgaga agccaaagct gctgcccctg gagctggaga agaccgccat ccagaactac 1680 accgtgacag agttccagcc cctgtactat gtggccgagt cttttaacga tgccaaggag 1740

aaggtgagaa atttcgccgc cacaatccct aggcccttca gtgtgcgtta cgacccttat 1800

acccagagga tcgaggtgct ggataataca cagcagctga agatcctggc tgactcaatc 1860

aatagcgaaa tcggaatcct gtgctccgcc ctgcagaaaa tcaaatgaga attcaaggcc 1920

tctcgagcct ctagaactat agtgagtcgt attacgtaga tccagacatg ataagataca 1980

ttgatgagtt tggacaaacc acaactagaa tgcagtgaaa aaaatgcttt atttgtgaaa 2040

tttgtgatgc tattgcttta tttgtaacca ttataagctg caataaacaa gttaacaaca 2100

acaattgcat tcattttatg tttcaggttc agggggaggt gtgggaggtt ttttaa 2156

<210> SEQ ID NO 53
<211> LENGTH: 1356
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

atgtccactg cggtcctgga aaacccaggc ttgggcagga aactctctga ctttggacag 60

gaaacaagct atattgaaga caactgcaat caaaatggtg ccatatcact gatcttctca 120

ctcaaagaag aagttggtgc attggccaaa gtattgcgct tatttgagga gaatgatgta 180

aacctgaccc acattgaatc tagaccttct cgtttaaaga aagatgagta tgaatttttc 240

acccatttgg ataaacgtag cctgcctgct ctgacaaaca tcatcaagat cttgaggcat 300

gacattggtg ccactgtcca tgagctttca cgagataaga agaaagacac agtgccctgg 360

ttcccaagaa ccattcaaga gctggacaga tttgccaatc agattctcag ctatggagcg 420

gaactggatg ctgaccaccc tggttttaaa gatcctgtgt accgtgcaag acggaagcag 480

tttgctgaca ttgcctacaa ctaccgccat gggcagccca tccctcgagt ggaatacatg 540

gaggaagaaa agaaaacatg ggcacagtg ttcaagactc tgaagtcctt gtataaaacc 600

catgcttgct atgagtacaa tcacattttt ccacttcttg aaaagtactg tggcttccat 660

gaagataaca ttccccagct ggaagacgtt tctcaattcc tgcagacttg cactggtttc 720

cgcctccgac ctgtggctgg cctgctttcc tctcgggatt tcttgggtgg cctggccttc 780

cgagtcttcc actgcacaca gtacatcaga catggatcca agcccatgta tacccccgaa 840

cctgacatct gccatgagct gttgggacat gtgcccttgt tttcagatcg cagctttgcc 900

cagttttccc aggaaattgg ccttgcctct ctgggtgcac ctgatgaata cattgaaaag 960

ctcgccacaa tttactggtt tactgtggag tttgggctct gcaaacaagg agactccata 1020

aaggcatatg gtgctgggct cctgtcatcc tttggtgaat tacagtactg cttatcagag 1080

aagccaaagc ttctccccct ggagctggag aagacagcca tccaaaatta cactgtcacg 1140

gagttccagc ccctgtatta cgtggcagag agttttaatg atgccaagga gaaagtaagg 1200

aactttgctg ccacaatacc tcggcccttc tcagttcgct acgacccata cacccaaagg 1260

attgaggtct tggacaatac ccagcagctt aagattttgg ctgattccat taacagtgaa 1320

attggaatcc tttgcagtgc cctccagaaa ataaag 1356

<210> SEQ ID NO 54
<211> LENGTH: 173
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 54

actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc 60

aaaatcaacg ggactttcca aaatgtcgta ataaccccgc cccgttgacg caaatgggcg 120

gtaggcgtgt acggtgggag gtctatataa gcagagctcg tttagtgaac cgt 173

<210> SEQ ID NO 55
<211> LENGTH: 100
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 55

ccaaaatcaa cgggactttc caaaatgtcg taataacccc gccccgttga cgcaaatggg 60

cggtaggcgt gtacggtggg aggtctatat aagcagagct 100

<210> SEQ ID NO 56
<211> LENGTH: 380
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 56

ggcattgatt attgactagt tattaatagt aatcaattac ggggtcatta gttcatagcc 60

catatatgga gttccgcgtt acataactta cggtaaatgg cccgcctggc tgaccgccca 120

acgacccccg cccattgacg tcaataatga cgtatgttcc catagtaacg ccaataggga 180

ctttccattg acgtcaatgg gtggagtatt tacggtaaac tgcccacttg gcagtacatc 240

aagtgtatca tatgccaagt ccgcccccta ttgacgtcaa tgacggtaaa tggcccgcct 300

ggcattatgc ccagtacatg accttacggg actttcctac ttggcagtac atctacgtat 360

tagtcatcgc tattaccatg 380

<210> SEQ ID NO 57
<211> LENGTH: 1246
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 57

tcgaggtgag ccccacgttc tgcttcactc tccccatctc ccccccctcc ccacccccaa 60

ttttgtattt atttattttt taattatttt gtgcagcgat gggggcgggg gggggggggg 120

ggcgcgcgcc aggcggggcg gggcggggcg aggggcgggg cggggcgagg cggagaggtg 180

cggcggcagc caatcagagc ggcgcgctcc gaaagtttcc ttttatggcg aggcggcggc 240

ggcggcggcc ctataaaaag cgaagcgcgc ggcgggcggg agtcgctgcg cgctgccttc 300

gccccgtgcc ccgctccgcc gccgcctcgc gccgcccgcc ccggctctga ctgaccgcgt 360

tactcccaca ggtgagcggg cgggacggcc cttctcctcc gggctgtaat tagcgcttgg 420

tttaatgacg gcttgtttct tttctgtggc tgcgtgaaag ccttgagggg ctccgggagg 480

gccctttgtg cggggggagc ggctcggggg gtgcgtgcgt gtgtgtgtgc gtggggagcg 540

ccgcgtgcgg ctccgcgctg cccggcggct gtgagcgctg cgggcgcggc gcggggcttt 600

gtgcgctccg cagtgtgcgc gaggggagcg cggccggggg cggtgccccg cggtgcgggg 660

ggggctgcga ggggaacaaa ggctgcgtgc ggggtgtgtg cgtggggggg tgagcagggg 720

-continued

gtgtgggcgc gtcggtcggg ctgcaacccc ccctgcaccc ccctccccga gttgctgagc 780

acggcccggc ttcgggtgcg gggctccgta cggggcgtgg cgcggggctc gccgtgccgg 840

gcggggggtg gcggcaggtg gggtgccgg gcggggcggg gccgcctcgg gccggggagg 900

gctcggggga ggggcgcggc ggcccccgga gcgccggcgg ctgtcgaggc gcggcgagcc 960

gcagccattg ccttttatgg taatcgtgcg agagggcgca gggacttcct ttgtcccaaa 1020

tctgtgcgga gccgaaatct gggaggcgcc gccgcacccc ctctagcggg cgcggggcga 1080

agcggtgcgg cgccggcagg aaggaaatgg gcggggaggg ccttcgtgcg tcgccgcgcc 1140

gccgtcccct tctccctctc cagcctcggg gctgtccgcg gggggacggc tgccttcggg 1200

ggggacgggg cagggcgggg ttcggcttct ggcgtgtgac cggcgg 1246

<210> SEQ ID NO 58
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 58

gaattcgggc ggagttaggg cggagccaat cagcgtgcgc cgttccgaaa gttgcctttt 60

atggctgggc ggagaatggg cggtgaacgc cgatgattat ataaggacgc gccgggtgtg 120

gcacagctag ttccgtcgca gccgggattt gggtcgcggt tcttgtttgt ggatccctgt 180

gatcgtgatc atcacttgtg a 201

<210> SEQ ID NO 59
<211> LENGTH: 953
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 59

aattcggtac cctagttatt aatagtaatc aattacgggg tcattagttc atagcccata 60

tatggagttc cgcgttacat aacttacggt aaatggcccg cctggctgac cgcccaacga 120

cccccgccca ttgacgtcaa taatgacgta tgttcccata gtaacgccaa tagggacttt 180

ccattgacgt caatgggtgg actatttacg gtaaactgcc cacttggcag tacatcaagt 240

gtatcatatg ccaagtacgc cccctattga cgtcaatgac ggtaaatggc ccgcctggca 300

ttatgcccag tacatgacct tatgggactt tcctacttgg cagtacatct acgtattagt 360

catcgctatt accatggtcg aggtgagccc cacgttctgc ttcactctcc ccatctcccc 420

cccctcccca cccccaattt tgtatttatt tatttttttaa ttattttgtg cagcgatggg 480

ggcggggggg gggggggggc gcgcgccagg cggggcgggg cggggcgagg ggcggggcgg 540

ggcgaggcgg agaggtgcgg cggcagccaa tcagagcggc gcgctccgaa agtttccttt 600

tatggcgagg cggcggcggc ggcggcccta taaaaagcga agcgcgcggc gggcgggagt 660

cgctgcgacg ctgccttcgc cccgtgcccc gctccgccgc cgcctcgcgc cgcccgcccc 720

ggctctgact gaccgcgtta ctcccacagg tgagcgggcg ggacggccct tctcctccgg 780

gctgtaatta gcgcttggtt taatgacggc ttgtttcttt tctgtggctg cgtgaaagcc 840

ttgaggggct ccgggagcta gagcctctgc taaccatgtt catgccttct tctttttcct 900

acagctcctg ggcaacgtgc tggttattgt gctgtctcat cattttggca aag 953

-continued

<210> SEQ ID NO 60
<211> LENGTH: 1766
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 60

gtaaatttta tggaatgtga atcataattc aatttttcaa catgcgttag gagggacatt 60

tcaaactctt ttttacccta gactttccta ccatcaccca gagtatccag ccaggagggg 120

aggggctaga gacaccagaa gtttagcagg gaggagggcg tagggattcg gggaatgaag 180

ggatgggatt cagactaggg ccaggaccca gggatggaga gaaagagatg agagtggttt 240

gggggcttgg tgacttagag aacagagctg caggctcaga ggcacacagg agtttctggg 300

ctcaccctgc ccccttccaa cccctcagtt cccatcctcc agcagctgtt tgtgtgctgc 360

ctctgaagtc cacactgaac aaacttcagc ctactcatgt ccctaaaatg ggcaaacatt 420

gcaagcagca aacagcaaac acacagccct ccctgcctgc tgaccttgga gctggggcag 480

aggtcagaga cctctctggg cccatgccac ctccaacatc cactcgaccc cttggaattt 540

cggtggagag gagcagaggt tgtcctggcg tggtttaggt agtgtgagag ggcttaagcg 600

tgaggctccg gtgcccgtca gtgggcagag cgcacatcgc ccacagtccc cgagaagttg 660

gggggagggg tcggcaattg aaccggtgcc tagagaaggt ggcgcggggt aaactgggaa 720

agtgatgtcg tgtactggct ccgccttttt cccgagggtg ggggagaacc gtatataagt 780

gcagtagtcg ccgtgaacgt tctttttcgc aacgggtttg ccgccagaac acaggtaagt 840

gccgtgtgtg gttcccgcgg gcctggcctc tttacgggtt atggcccttg cgtgccttga 900

attacttcca cctggctcca gtacgtgatt cttgatcccg agctggagcc aggggcgggc 960

cttgcgcttt aggagcccct tcgcctcgtg cttgagttga ggcctggcct gggcgctggg 1020

gccgccgcgt gcgaatctgg tggcaccttc gcgcctgtct cgctgctttc gataagtctc 1080

tagccattta aaatttttga tgacctgctg cgacgctttt tttctggcaa gatagtcttg 1140

taaatgcggg ccaggatctg cacactggta tttcggtttt tggggccgcg ggcggcgacg 1200

gggcccgtgc gtcccagcgc acatgttcgg cgaggcgggg cctgcgagcg cggccaccga 1260

gaatcggacg gggtagtct caagctggcc ggcctgctct ggtgcctggc ctcgcgccgc 1320

cgtgtatcgc cccgccctgg gcggcaaggc tggcccggtc ggcaccagtt gcgtgagcgg 1380

aaagatggcc gcttcccggc cctgctccag gggctcaaa atggaggacg cggcgctcgg 1440

gagagcgggc gggtgagtca cccacacaaa ggaaaggggc ctttccgtcc tcagccgtcg 1500

cttcatgtga ctccacggag taccgggcgc cgtccaggca cctcgattag ttctggagct 1560

tttggagtac gtcgtcttta ggttgggggg aggggtttta tgcgatggag tttccccaca 1620

ctgagtgggt ggagactgaa gttaggccag cttggcactt gatgtaattc tccttggaat 1680

ttgccctttt tgagtttgga tcttggttca ttctcaagcc tcagacagtg gttcaaagtt 1740

tttttcttcc atttcaggtg tcgtga 1766

<210> SEQ ID NO 61
<211> LENGTH: 82
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 61

```
gtaagggttt aagggatggt tggttggtgg ggtattaatg tttaattacc tggagcacct     60

gcctgaaatc actttttttc ag                                              82


<210> SEQ ID NO 62
<211> LENGTH: 95
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 62

cctctgctaa ccatgttcat gccttcttct ttttcctaca gctcctgggc aacgtgctgg     60

ttattgtgct gtctcatcat tttggcaaag aattc                                95


<210> SEQ ID NO 63
<211> LENGTH: 1356
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 63

atgtccaccg ctgtgctgga gaaccctggg ctggggagga aactgtcaga cttcgggcag     60

gagacttcat acattgagga taactgtaac cagaatggcg ccatctctct gatcttcagc    120

ctgaaggagg aagtgggcgc cctggcaaag gtgctgcgcc tgtttgagga gaacgacgtg    180

aatctgaccc acatcgagtc ccggccttct agactgaaga aggacgagta cgagttcttt    240

acccacctgg ataagcggtc cctgccagcc ctgacaaaca tcatcaagat cctgaggcac    300

gacatcggag caaccgtgca cgagctgtct cgggacaaga agaaggatac cgtgccctgg    360

ttccctcgga caatccagga gctggataga tttgccaacc agatcctgtc ttacggagca    420

gagctggacg cagatcaccc tggcttcaag gacccagtgt atcgggcccg gagaaagcag    480

tttgccgata tcgcctacaa ttataggcac ggacagccaa tccctcgcgt ggagtatatg    540

gaggaggaga agaagacctg ggcacagtg ttcaagaccc tgaagagcct gtacaagaca    600

cacgcctgct acgagtataa ccacatcttc cccctgctgg agaagtattg tggctttcac    660

gaggacaata tccctcagct ggaggacgtg agccagttcc tgcagacctg cacaggcttt    720

aggctgaggc cagtggcagg actgctgagc tcccgggact tcctgggagg actggccttc    780

agagtgtttc actgcaccca gtacatcagg cacggctcca agccaatgta tacaccagag    840

cccgacatct gtcacgagct gctgggccac gtgcccctgt ttagcgatag atccttcgcc    900

cagttttccc aggagatcgg actggcatct ctgggagcac ctgacgagta catcgagaag    960

ctggccacca tctattggtt cacagtggag tttggcctgt gcaagcaggg cgatagcatc   1020

aaggcctacg gagcaggact gctgtctagc ttcggcgagc tgcagtattg tctgtccgag   1080

aagccaaagc tgctgcccct ggagctggag aagaccgcca tccagaacta caccgtgaca   1140

gagttccagc ccctgtacta tgtggccgag tcttttaacg atgccaagga gaaggtgaga   1200

aatttcgccg ccacaatccc taggcccttc agcgtgcggt acgaccctta tacccagagg   1260

atcgaggtgc tggataatac acagcagctg aagatcctgg ctgactcaat caatagcgaa   1320

atcggaatcc tgtgctccgc cctgcagaaa atcaaa                             1356


<210> SEQ ID NO 64
<211> LENGTH: 1873
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
```

<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 64

gatcttcaat attggccatt agccatatta ttcattggtt atatagcata aatcaatatt 60

ggctattggc cattgcatac gttgtatcta tatcataata tgtacattta tattggctca 120

tgtccaatat gaccgccatg ttggcattga ttattgacta gttattaata gtaatcaatt 180

acggggtcat tagttcatag cccatatatg gagttccgcg ttacataact tacggtaaat 240

ggcccgcctg gctgaccgcc caacgacccc cgcccattga cgtcaataat gacgtatgtt 300

cccatagtaa cgccaatagg gactttccat tgacgtcaat gggtggagta tttacggtaa 360

actgcccact tggcagtaca tcaagtgtat catatgccaa gtccgccccc tattgacgtc 420

aatgacggta aatggcccgc ctggcattat gcccagtaca tgaccttacg ggactttcct 480

acttggcagt acatctacgt attagtcatc gctattacca tggtcgaggt gagccccacg 540

ttctgcttca ctctccccat ctcccccccc tccccacccc caattttgta tttatttatt 600

ttttaattat tttgtgcagc gatgggggcg gggggggggg ggggcgcgc gccaggcggg 660

gcggggcggg gcgaggggcg gggcggggcg aggcggagag gtgcggcggc agccaatcag 720

agcggcgcgc tccgaaagtt tcctttatg gcgaggcggc ggcggcggcg gccctataaa 780

aagcgaagcg cgcggcgggc gggagtcgct gcgacgctgc cttcgccccg tgccccgctc 840

cgccgccgcc tcgcgccgcc cgccccggct ctgactgacc gcgttactcc cacaggtgag 900

cgggcgggac ggcccttctc ctccgggctg taattagcgc ttggtttaat gacggcttgt 960

ttcttttctg tggctgcgtg aaagccttga ggggctccgg gagggccctt tgtgcggggg 1020

ggagcggctc gggggtgcg tgcgtgtgtg tgtgcgtggg gagcgccgcg tgcggcccgc 1080

gctgcccggc ggctgtgagc gctgcgggcg cggcgcgggg ctttgtgcgc tccgcagtgt 1140

gcgcgagggg agcgcggccg gggcggtgc cccgcggtgc ggggggggct gcgaggggaa 1200

caaaggctgc gtgcggggtg tgtgcgtggg ggggtgagca gggggtgtgg gcgcggcggt 1260

cgggctgtaa cccccccctg cacccccctc cccgagttgc tgagcacggc ccggcttcgg 1320

gtgcggggct ccgtacgggg cgtggcgcgg ggctcgccgt gccgggcggg gggtggcggc 1380

aggtgggggt gccgggcggg gcggggccgc ctcgggccgg ggagggctcg gggagggc 1440

gcggcggccc ccggagcgcc ggcggctgtc gaggcgcggc gagccgcagc cattgccttt 1500

tatggtaatc gtgcgagagg gcgcagggac ttcctttgtc ccaaatctgt gcggagccga 1560

aatctgggag gcgccgccgc acccctcta gcgggcgcgg ggcgaagcgg tgcggcgccg 1620

gcaggaagga aatgggcggg gagggccttc gtgcgtcgcc gcgccgccgt ccccttctcc 1680

ctctccagcc tcggggctgt ccgcgggggg acggctgcct tcgggggga cggggcaggg 1740

cggggttcgg cttctggcgt gtgaccggcg gctctagagc ctctgctaac catgttcatg 1800

ccttcttctt tttcctacag ctcctgggca acgtgctggt tattgtgctg tctcatcatt 1860

ttggcaaaga att 1873

<210> SEQ ID NO 65
<211> LENGTH: 1061
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 65

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```
tagggaggtc ctgcacgtta cataacttac ggtaaatggc ccgcctggct gaccgcccaa     60

cgacccccgc ccattgacgt caataatgac gtatgttccc atagtaacgc caatagggac    120

tttccattga cgtcaatggg tggagtattt acggtaaact gcccacttgg cagtacatca    180

agtgtatcat atgccaagta cgccccctat tgacgtcaat gacggtaaat ggcccgcctg    240

gcattatgcc cagtacatga ccttatggga ctttcctact tggcagtaca tctacgtatt    300

agtcatcgct attaccatgg tcgaggtgag ccccacgttc tgcttcactc tccccatctc    360

ccccccctcc ccacccccaa ttttgtattt atttattttt taattatttt gtgcagcgat    420

gggggcgggg gggggggggg gcgcgcgcca ggcggggcgg ggcggggcga ggggcggggc    480

ggggcgaggc ggagaggtgc ggcggcagcc aatcagagcg gcgcgctccg aaagtttcct    540

tttatggcga ggcggcggcg gcggcggccc tataaaaagc gaagcgcgcg gcgggcggga    600

gtcgctgcgc gctgccttcg ccccgtgccc cgctccgccg ccgcctcgcg ccgcccgccc    660

cggctctgac tgaccgcgtt actaaaacag gtaagtccgg cctccgcgcc gggttttggc    720

gcctcccgcg ggcgcccccc tcctcacggc gagcgctgcc acgtcagacg aagggcgcag    780

cgagcgtcct gatccttccg cccggacgct caggacagcg gcccgctgct cataagactc    840

ggccttagaa ccccagtatc agcagaagga cattttagga cgggacttgg gtgactctag    900

ggcactggtt ttctttccag agagcggaac aggcgaggaa aagtagtccc ttctcggcga    960

ttctgcggag ggatctccgt ggggcggtga acgccgatga tgcctctact aaccatgttc   1020

atgttttctt tttttttcta caggtcctgg gtgacgaaca g                       1061
```

```
<210> SEQ ID NO 66
<211> LENGTH: 170
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 66

cgatgctcta atctctctag acaaggttca tatttgtatg ggttacttat tctctctttg     60

ttgactaagt caataatcag aatcagcagg tttgcagtca gattggcagg gataagcagc    120

ctagctcagg agaagtgagt ataaaagccc caggctggga gcagccatca               170
```

```
<210> SEQ ID NO 67
<211> LENGTH: 254
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 67

gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg     60

ggctaagtcc acctcgagcc atggcgatgc tctaatctct ctagacaagg ttcatatttg    120

tatgggttac ttattctctc tttgttgact aagtcaataa tcagaatcag caggtttgca    180

gtcagattgg cagggataag cagcctagct caggagaagt gagtataaaa gccccaggct    240

gggagcagcc atca                                                      254
```

```
<210> SEQ ID NO 68
<211> LENGTH: 592
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide
```

<400> SEQUENCE: 68

gtaaatttta tggaatgtga atcataattc aatttttcaa catgcgttag gagggacatt 60

tcaaactctt ttttacccta gactttccta ccatcaccca gagtatccag ccaggagggg 120

aggggctaga gacaccagaa gtttagcagg gaggagggcg tagggattcg gggaatgaag 180

ggatgggatt cagactaggg ccaggaccca gggatggaga gaaagagatg agagtggttt 240

gggggcttgg tgacttagag aacagagctg caggctcaga ggcacacagg agtttctggg 300

ctcaccctgc ccccttccaa cccctcagtt cccatcctcc agcagctgtt tgtgtgctgc 360

ctctgaagtc cacactgaac aaacttcagc ctactcatgt ccctaaaatg ggcaaacatt 420

gcaagcagca aacagcaaac acacagccct ccctgcctgc tgaccttgga gctggggcag 480

aggtcagaga cctctctggg cccatgccac ctccaacatc cactcgaccc cttggaattt 540

cggtggagag gagcagaggt tgtcctggcg tggtttaggt agtgtgagag gg 592

<210> SEQ ID NO 69
<211> LENGTH: 205
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 69

aatgactcct ttcggtaagt gcagtggaag ctgtacactg cccaggcaaa gcgtccgggc 60

agcgtaggcg ggcgactcag atcccagcca gtggacttag cccctgtttg ctcctccgat 120

aactggggtg accttggtta atattcacca gcagcctccc ccgttgcccc tctggatcca 180

ctgcttaaat acggacgagg acagg 205

<210> SEQ ID NO 70
<211> LENGTH: 423
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 70

gctctaaccc actctgatct cccagggcgg cagtaagtct tcagcatcag gcattttggg 60

gtgactcagt aaatggtaga tcttgctacc agtggaacag ccactaagga ttctgcagtg 120

agagcagagg gccagctaag tggtactctc ccagagactg tctgactcac gccacccccct 180

ccaccttgga cacaggacgc tgtggtttct gagccaggta caatgactcc tttcggtaag 240

tgcagtggaa gctgtacact gcccaggcaa agcgtccggg cagcgtaggc gggcgactca 300

gatcccagcc agtggactta gcccctgttt gctcctccga taactggggt gaccttggtt 360

aatattcacc agcagcctcc cccgttgccc ctctggatcc actgcttaaa tacggacgag 420

gac 423

<210> SEQ ID NO 71
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 71

gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 60

```
ggctaagtcc ac                                                        72


<210> SEQ ID NO 72
<211> LENGTH: 913
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 72

tagggaggtc ctgcacagaa ggggaggagg gggcagcagc tgtctgacca ctgttggtct     60

tgcaacttgt gtccccaggt taatttttaa aaagcagtca aaagtccaag tggcccttgg    120

cagcatttac tctctctgtt tgctctggtt aataatctca ggagcacaaa cattcctgga    180

ggcaggagaa gaaatcaaca tcctggactt atcctctggg cctctcccca cccccaggat    240

tgtaactgaa atgcttcact ggtgctcctt ttgttttaag gcattggatc ttcatagcta    300

ctgatcgtgc ccaagcacac agtatctgca gcaaccactt aggcctccag gaatgtggtg    360

accattgacc ctaattcatt ccccttcatg gatcctatgt aaccatcctc caaaaagagc    420

tttcgcaaac tcaaataaac acaggaaagg aagaccttct tatctttgag agtatatgtt    480

tagccctata gctctaaccc actctgatct cccagggcgg cagtaagtct tcagcatcag    540

gcattttggg gtgactcagt aaatggtaga tcttgctacc agtggaacag ccactaagga    600

ttctgcagtg agagcagagg gccagctaag tggtactctc ccagagactg tctgactcac    660

gccaccccct ccaccttgga cacaggacgc tgtggtttct gagccaggta caatgactcc    720

tttcggtaag tgcagtggaa gctgtacact gcccaggcaa agcgtccggg cagcgtaggc    780

gggcgactca gatcccagcc agtggactta gcccctgttt gctcctccga taactggggt    840

gaccttggtt aatattcacc agcagcctcc cccgttgccc ctctggatcc actgcttaaa    900

tacggacgag gac                                                       913


<210> SEQ ID NO 73
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 73

gtagataagt agcatggcgg gttaatcatt aactaca                              37


<210> SEQ ID NO 74
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 74

ggaggggtgg agtcgtgacg tgaattacgt catagggtta gggagg                    46


<210> SEQ ID NO 75
<211> LENGTH: 182
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 75

gtagataagt agcatggcgg gttaatcatt aactacaagg aacccctagt gatggagttg     60
```

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gccactccct ctctgcgcgc tcgctcgctc actgaggccg ggcgaccaaa ggtcgcccga 120

cgcccgggct ttgcccgggc ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc 180

aa 182

<210> SEQ ID NO 76
<211> LENGTH: 191
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 76

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<210> SEQ ID NO 77
<211> LENGTH: 3230
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 77

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caatcctttc ttctgggtat caaaatgaca agcttgtaag aaactgtcct ctttcggctt 2880

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<210> SEQ ID NO 78
<211> LENGTH: 3637
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 78

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<210> SEQ ID NO 79
<211> LENGTH: 3776
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 79

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<210> SEQ ID NO 80
<211> LENGTH: 4186
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 80

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<210> SEQ ID NO 81
<211> LENGTH: 3713
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 81

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aatccacaaa ttatattaat aacaaacaaa gtagtgtcgt gttatatagt aaatgtgaat 3660

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<210> SEQ ID NO 82
<211> LENGTH: 4139
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 82

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cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgcag agagggagtg 120

gccaactcca tcactagggg ttcctggagg ggtggagtcg tgacgtgaat tacgtcatag 180

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<210> SEQ ID NO 83
<211> LENGTH: 1353
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 83

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aaggaggaag tgggcgccct ggcaaaggtg ctgcgcctgt ttgaggagaa cgacgtgaat 180

ctgacccaca tcgagtcccg gccttctaga ctgaagaagg acgagtacga gttctttacc 240

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<210> SEQ ID NO 84
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 84

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cctctttgca gagacccagc caccatacta gtacctagag aactggctgg atttcagccc 180

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<210> SEQ ID NO 85
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 85

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cgatacctcc gggcttttgc tcatgttcgc ctcatagggt catctgggtg gttgcctaag    240

gaaaagtatg tcatggagac taacttgctt ggcattgaat aaaaggtgag ttgagagtgg    300

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tggactgttc atgtctatcc actgctacgt cagggcaaca cccactgaga gtgaccttgt    660

agactgcagt gggagacacc cttcaaaacc tctcctctcc tgtcctgaga gccaggttaa    720

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<210> SEQ ID NO 86
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 86

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gaaatgctgg tatttccagt ctcctaaggc tactaagaaa tatgacttta tttagaggcg    180

aggaaaatgc ccaggaagtc aactgatgag actagtctta acaagttgag gatacagaaa    240

gttggggatc tgagctgcta ccaacatctg tgtgtctttg ggtggctcat tggtatcctc    300

tgcctattgg ctttatcttc tgtacactga aaggaaatgg ctggtcctta gtcacctggg    360

gtgggagtcc ctatctctcc agggatactt attcaatcct ttcttctggg tatcaaaatg    420

acaagcttgt aagaaactgt cctctttcgg ctttcaggag gtgatgtcgc atgaagagaa    480

tttggggggg gggacttact cagaaccaag gagggagaaa ttaaacagag agggaaatga    540

acaggagtta gcccggagcc tgaagcacct tggggattat gctgggggtg gagggaatcc    600

attgtcctcc ctagggaggg cttgcagaac atgttctttt ctgtgatatt tgtactttcc    660

ccagattgca aatcatggtt tgtacactga gattcagtct ctggaggtaa tatgcctttt    720

ctagcttttc cttggacagg actaaggggt tgagggttgc ctggagtcag agaaatttgt    780

gttaaagaag gttgatatga                                                800
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We claim:

1. A recombinant adeno-associated virus (rAAV) comprising: (a) an AAV capsid comprising an AAV capsid protein; and (b) an rAAV genome comprising: (1) an editing element for editing a target locus in a phenylalanine hydroxylase (PAH) gene, comprising a PAH coding sequence operably linked to a transcriptional regulatory element, wherein the PAH coding sequence comprises the nucleotide sequence set forth in SEQ ID NO: 28; (ii) a 5' homology arm nucleotide sequence positioned 5' of the editing element, having homology to a first genomic region 5' to the target locus; and (iii) a 3' homology arm nucleotide sequence positioned 3' of the editing element, having homology to a second genomic region 3' to the target locus.

2. The rAAV of claim **1**, wherein the transcriptional regulatory element is capable of mediating transcription in a hepatocyte, a renal cell, a brain cell, a pituitary gland cell, an adrenal gland cell, a pancreatic cell, a urinary bladder cell, a gallbladder cell, a colon cell, a small intestine cell, or a breast cell, optionally wherein:

the transcriptional regulatory element is endogenous to the PAH gene; or the transcriptional regulatory element is exogenous to the PAH gene, optionally wherein:

the transcriptional regulatory element is liver specific, optionally wherein the transcriptional regulatory element comprises one or more elements selected from the group consisting of a human albumin promoter, a human transthyretin (TTR) promoter, a human ApoE/C-I hepatic control region (HCR) 1 or 2, a human ApoH promoter, a human SERPINA1 (hAAT) promoter, and a hepatic specific regulatory module thereof;

the transcriptional regulatory element comprises a nucleotide sequence at least 90% identical to a sequence selected from the group consisting of SEQ ID NO: 25, 26, 27, and 69;

the transcriptional regulatory element comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 27;

the transcriptional regulatory element comprises the nucleotide sequence set forth in SEQ ID NO: 27; or

the nucleotide sequence of the transcriptional regulatory element consists of the nucleotide sequence set forth in SEQ ID NO: 27.

3. The rAAV of claim **1**, wherein the editing element further comprises an intron element positioned 5' to the PAH coding sequence and 3' to the transcriptional regulatory element, optionally wherein the intron element is an exogenous intron element, optionally an SV40 intron element, optionally wherein:

the SV40 intron element comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 29;

the SV40 intron element comprises the nucleotide sequence set forth in SEQ ID NO: 29; or the nucleotide sequence of the SV40 intron element consists of the nucleotide sequence set forth in SEQ ID NO: 29.

4. The rAAV of claim **1**, wherein the editing element further comprises a polyadenylation sequence 3' to the PAH coding sequence, optionally wherein the polyadenylation sequence is an exogenous polyadenylation sequence, optionally an SV40 polyadenylation sequence, optionally wherein

the SV40 polyadenylation sequence comprises a nucleotide sequence at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 31;

the SV40 polyadenylation sequence comprises the nucleotide sequence set forth in SEQ ID NO: 31; or

the nucleotide sequence of the SV40 polyadenylation sequence consists of the nucleotide sequence set forth in SEQ ID NO: 31.

5. The rAAV of claim **1**, wherein:

the nucleotide sequence 5' to the target locus is in an intron of a PAH gene, optionally in intron 1 of a PAH gene; and/or

the nucleotide sequence 3' to the target locus is in an intron of a PAH gene, optionally in intron 1 of a PAH gene.

6. The rAAV of claim **1**, wherein the PAH gene is a human PAH gene, optionally wherein the human PAH gene is wild-type or a variant PAH gene.

7. The rAAV of claim **1**, wherein the editing element comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: 25, 26, 27, 29, 31, 50, 51, 52, 69, and 70.

8. The rAAV of claim **1**, wherein:

the 5' homology arm nucleotide sequence is at least 90% identical to the first genomic region;

the 3' homology arm nucleotide sequence is at least 90% identical to the second genomic region;

the first genomic region is located in a first editing window, and the second genomic region is located in a second editing window, optionally wherein:

the first editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37;

the second editing window consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38;

the first genomic region consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 37; and/or

the second genomic region consists of the region of the human genome corresponding to the nucleotide sequence set forth in SEQ ID NO: 38.

9. The rAAV of claim **1**, wherein:

each of the 5' and the 3' homology arm nucleotide sequences independently has a length of about 100 to about 2000 nucleotides;

the 5' homology arm comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 23;

the nucleotide sequence of the 5' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 23;

the 3' homology arm comprises a nucleotide sequence that is at least 90% identical to the nucleotide sequence set forth in SEQ ID NO: 24; and/or

the nucleotide sequence of the 3' homology arm consists of the nucleotide sequence set forth in SEQ ID NO: 24.

10. The rAAV of claim **1**, wherein the rAAV genome comprises a nucleotide sequence that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 43.

11. The rAAV of claim **1**, wherein the rAAV genome further comprises a 5' inverted terminal repeat (5' ITR) nucleotide sequence 5' of the 5' homology arm nucleotide sequence, and a 3' inverted terminal repeat (3' ITR) nucleotide sequence 3' of the 3' homology arm nucleotide sequence, optionally wherein:

the 5' ITR nucleotide sequence is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 14, and/or the 3' ITR nucleotide sequence is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 18; and/or

the rAAV genome comprises the nucleotide sequence set forth in SEQ ID NO: 73, 74, 75, or 76.

12. The rAAV of claim **1**, wherein the rAAV genome comprises a nucleotide sequence that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 45.

13. The rAAV of claim **1**, wherein:

the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, optionally wherein:

(i) the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ

ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is Gor Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(ii) (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G; (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; (c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; (d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or (e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; and/or

(iii) the capsid protein comprises the amino acid sequence of amino acids 203-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17;

the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, optionally wherein:

(i) the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(ii) (a) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G; (b) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; (c) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; (d) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or (e) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; and/or

(iii) the capsid protein comprises the amino acid sequence of amino acids 138-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 16, or 17; and/or

the AAV capsid protein comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17, optionally wherein:

(i) the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T; the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 68 of SEQ ID NO: 16 is V; the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L; the amino acid in the capsid protein corresponding to amino acid 151 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 160 of SEQ ID NO: 16 is D; the amino acid in the capsid protein corresponding to amino acid 206 of SEQ ID NO: 16 is C; the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H; the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q;

the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A; the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N; the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID

NO: 16 is I; the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 590 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G or Y; the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; or, the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G;

(ii) (a) the amino acid in the capsid protein corresponding to amino acid 2 of SEQ ID NO: 16 is T, and the amino acid in the capsid protein corresponding to amino acid 312 of SEQ ID NO: 16 is Q; (b) the amino acid in the capsid protein corresponding to amino acid 65 of SEQ ID NO: 16 is I, and the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is Y; (c) the amino acid in the capsid protein corresponding to amino acid 77 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 690 of SEQ ID NO: 16 is K; (d) the amino acid in the capsid protein corresponding to amino acid 119 of SEQ ID NO: 16 is L, and the amino acid in the capsid protein corresponding to amino acid 468 of SEQ ID NO: 16 is S; (e) the amino acid in the capsid protein corresponding to amino acid 626 of SEQ ID NO: 16 is G, and the amino acid in the capsid protein corresponding to amino acid 718 of SEQ ID NO: 16 is G; (f) the amino acid in the capsid protein corresponding to amino acid 296 of SEQ ID NO: 16 is H, the amino acid in the capsid protein corresponding to amino acid 464 of SEQ ID NO: 16 is N, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 681 of SEQ ID NO: 16 is M; (g) the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 687 of SEQ ID NO: 16 is R; (h) the amino acid in the capsid protein corresponding to amino acid 346 of SEQ ID NO: 16 is A, and the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R; or (i) the amino acid in the capsid protein corresponding to amino acid 501 of SEQ ID NO: 16 is I, the amino acid in the capsid protein corresponding to amino acid 505 of SEQ ID NO: 16 is R, and the amino acid in the capsid protein corresponding to amino acid 706 of SEQ ID NO: 16 is C; and/or

(iii) the capsid protein comprises the amino acid sequence of amino acids 1-736 of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, or 17.

14. A pharmaceutical composition comprising an rAAV of claim **1**.

15. The rAAV of claim **1**, wherein the editing element comprises a nucleotide sequence that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 52.

16. The rAAV of claim **1**, comprising:

(a) an AAV capsid comprising: a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 16; a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 16; and/or a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 16; and

(b) an rAAV genome comprising a nucleotide sequence that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 43.

17. The rAAV of claim **1**, comprising:

(a) an AAV capsid comprising: a capsid protein comprising the amino acid sequence of amino acids 203-736 of SEQ ID NO: 16; a capsid protein comprising the amino acid sequence of amino acids 138-736 of SEQ ID NO: 16; and/or a capsid protein comprising the amino acid sequence of amino acids 1-736 of SEQ ID NO: 16; and

(b) an rAAV genome comprising a nucleotide sequence that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 45.

18. A polynucleotide comprising the nucleic acid sequence set forth in SEQ ID NO: 43, 45, 51, or 52.

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